NSAIDs & Hematopoietic Drugs

(NSAIDS & HEMATOPOIETIC DRUGS)

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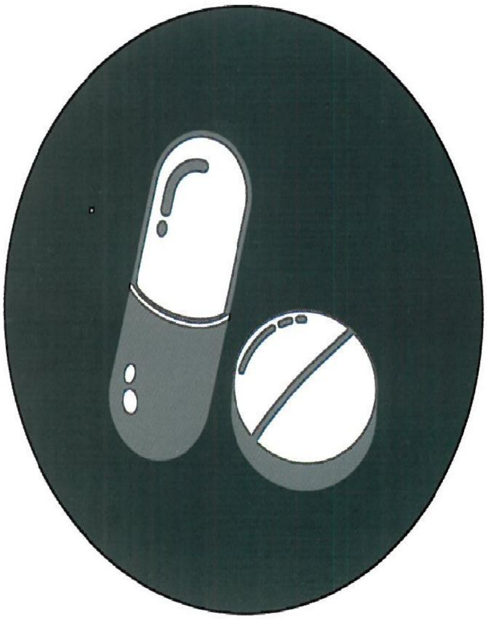
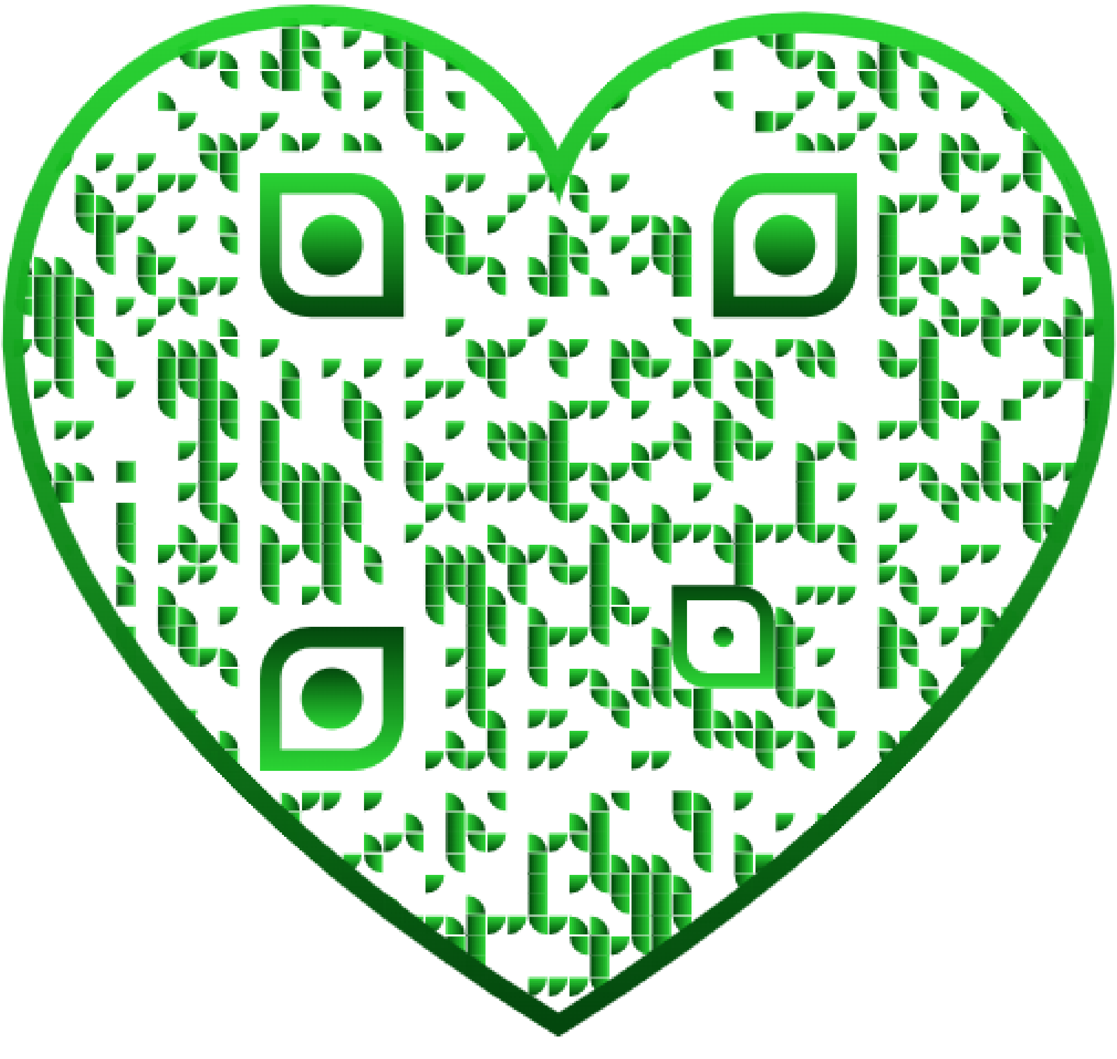
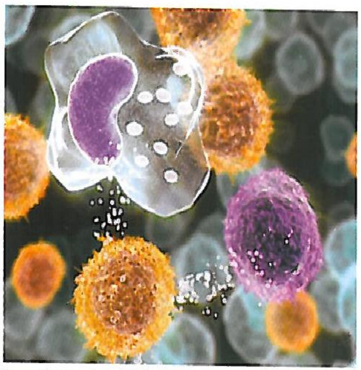




Non-steroidal Anti-inflammatory Drugs (NSAIDs)

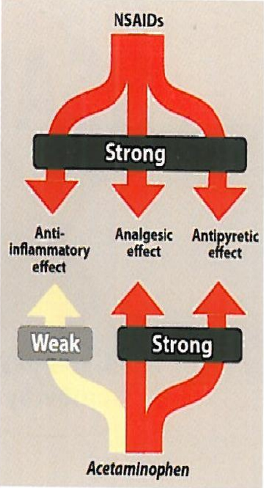
➢ Overview:-

- **Inflammation**;
  - **Inflammation** is a ***normal part*** of the ***complex*** **biological response** of **body tissues** to ***harmful*** **stimuli** *caused by* **physical trauma, noxious chemicals** or **microbiologic agents.**
  - **Inflammation** is the **body's effort** to ***inactivate*** or ***destroy*** invading **organisms**, ***remove*** **irritants** and ***set*** the **stage** *for* **tissue repair.**
  - **Inflammation** is *sometimes* ***triggered by*** an **innocuous agent**, *such as* **pollen**, or by an **autoimmune response**, as in **rheumatoid arthritis.**
  - **Inflammation** is ***triggered by*** the ***release*** of **chemical mediators** from **injured tissues** and **migrating cells.**
  - The ***specific*** **chemical mediators** ***vary*** with the **type of inflammation** and *include*;



    - ***Amines***; *such as* **histamine** and **5-hydroxytryptamine (serotonin).**
    - ***Lipids***; *such as* **prostaglandins, thromboxanes** and **leukotrienes.**
    - ***Small peptides***; such as **bradykinin.**
    - ***Larger peptides***; such as **interleukin-1** and **tumor necrosis factor α (TNF-α).**
  - **Anti-inflammatory drugs** *act by* ***interfere*** with the **action** of ***specific*** **mediator** ***important in*** **inflammation.**

- **Non-steroidal Anti-inflammatory Drugs (NSAIDs)**;
  - **NSAIDs**; are a ***group*** of **chemically** ***dissimilar*** **agents** that ***have*** **analgesic** (*pain-killing*) and **antipyretic** (*fever-reducing*) and **anti-inflammatory** ***effects.***
  - The ***term*** **non-steroidal** to ***differentiate*** *these* **drugs** *from* **steroidal anti-inflammatory** (***corticosteroids***).
  - **NSAIDs**; *such as* **Aspirin, Ibuprofen** and **Naproxen**, ***all*** are **widely** ***available*** **over the counter** (**OTC**).
  - **Paracetamol (Acetaminophen)** is ***generally not*** **considered** an **NSAID** because *it has **only little*** **anti-inflammatory activity.**
  - The **NSAIDs** *act by **inhibiting*** the **synthesis** of **prostaglandins.** Thus, an ***understanding*** of **NSAIDs** ***requires*** **comprehension** of the ***actions*** and ***biosynthesis*** of **Prostaglandins (PGs)** [These compounds referred to as **eicosanoids**].

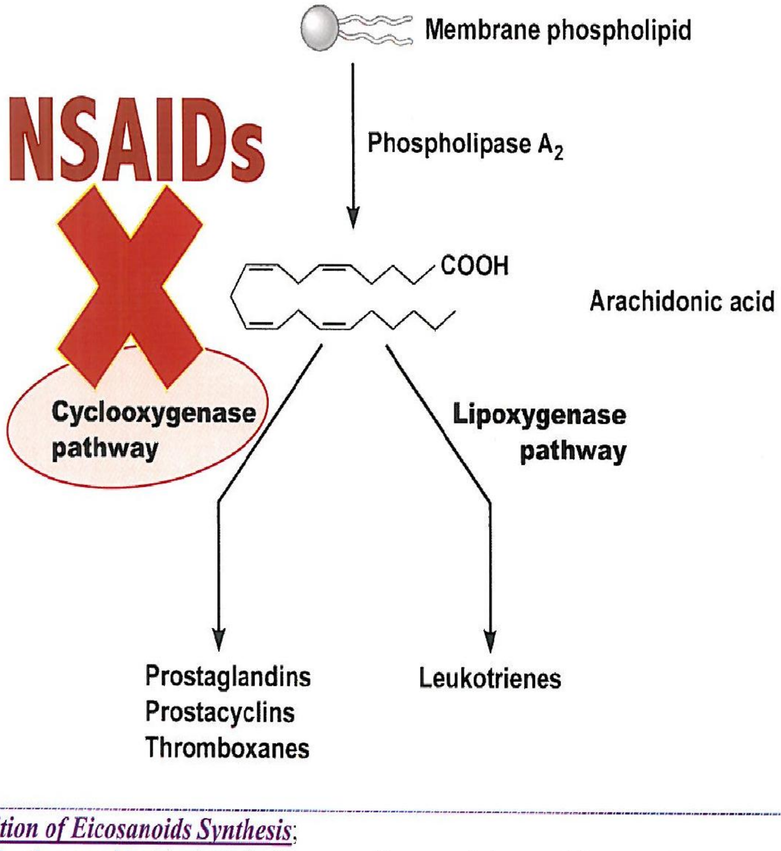


➢ Eicosanoids (see Autacoids chapter *for full illustration*):-

- **Eicosanoids** are ***oxygenation*** products of **polyunsaturated long-chain (20 C atom) fatty acids.**
- They have specific effects and they are ***multiple subfamilies***; e.g. **Prostaglandins (PGs), Thromboxanes (TXs)** and **Leukotrienes (LTs).**
- The **PGs** and **TXs** are collectively ***identified as*** **Prostanoids.**
- **Prostaglandins** were originally shown to be synthesized in the ***prostate gland***, **thromboxanes** from ***platelets*** (thrombocytes) and **leukotrienes** from ***leukocytes***, hence the derivation of their names.

- *Eicosanoids biosynthesis*;
  - **Eicosanoids** are ***not*** **stored** *within cells*, ***but*** are **synthesized as required.**
  - **Two main pathways** are involved in the **biosynthesis of eicosanoids;**
    1) The **prostaglandins** and **thromboxanes** are ***synthesized*** by the **cyclic pathway.**
    2) The **leukotrienes** are ***synthesized*** by the **linear pathway.**

- *Eicosanoids Biosynthesis Steps*;
  1) **20-carbon atoms fatty acid (arachidonic acid; AA) formation**;
     - **Eicosanoid biosynthesis *begins*** when a **cell is activated** by; mechanical trauma, cytokines, growth factors or other stimuli.
     - **This triggers** ⇨ ***release*** of a **phospholipase** at the **cell membrane**.
     - The **phospholipase *catalyzes* ester hydrolysis** of **phospholipid** (by phospholipase A_2; PLA) or diacylglycerol (by phospholipase C; PLC).
     - **This *frees*** a **20-carbon fatty acid (arachidonic acid; AA)**.
  2) **Prostanoids formation (cyclooxygenase pathway)**;
     - **The cyclic pathway** is ***initiated*** through the action of **prostaglandin G/H synthase** (*also called* **prostaglandin-endoperoxide synthase**).
     - This enzyme possesses ***two activities***, **cyclooxygenase (COX)** and **peroxidase**.
     - There are ***two forms*** of **COX** activity in humans, **COX-1** and **COX-2**.
     - **COX-1** (**prostaglandin synthase-1; PGS-1**) is ***expressed constitutively*** in **gastric mucosa, kidney, platelets, and vascular endothelial cells.**
     - **COX-2** (**prostaglandin synthase-2; PGS-2**) is ***inducible and is expressed*** in **macrophages** and **monocytes *in response*** to **inflammation.**
     - ***Both* COX-1 & COX-2 *catalyse*** the **2-step conversion** of **arachidonic acid *to* prostanoids**, including **prostaglandins (PGs)**, **prostacyclin (PGI_2)** and **thromboxane (TXA_2)**.
  3) **Leukotrienes formation (lipoxygenase pathway)**;
     - **The linear pathway** is ***initiated*** through the action of **lipoxygenase (LOX) enzymes** of which there are ***three forms***, **5-LOX**, **12-LOX** and **15-LOX**.
     - ***The most actively investigated*** **leukotrienes** are those ***produced*** by the **5-LOX**.
     - The **leukotrienes** are ***synthesized*** by several different cell types including **white blood cells (leukocytes)**, **mast cells**, **lung**, **spleen**, **brain** and **heart**.



- *Inhibition of Eicosanoids Synthesis*;
  - **Corticosteroids *block all*** the known **pathways** of **eicosanoid synthesis**.
  - **Non-steroidal anti-inflammatory drugs (NSAIDs)**, ***blocks*** both **Prostaglandins (PGs)** and **Thromboxane-A_2 (TXA_2)** **formation** by ***inhibiting*** **COX** activity.
  - **5-LOX inhibitor** (e.g. **Zileuton**) and ***selective antagonists*** **leukotrienes receptor** (**LTC_4, LTD_4** and **LTE_4**) (**Zafirlukast**, **Montelukast** & **Pranlukast**), are used in **bronchial asthma**.

- ***Major Roles of Eicosanoids***;
  - **Prostaglandins (PGs)**;
    - *Modulate* **pain, inflammation** and **fever**.
    - *Control* **acid secretion** and **mucus production** *in the GIT*.
    - *Control* **renal blood flow**.
    - *Control* **uterine contractions**.
  - **Prostacyclin (PGI_2)**;
    - *Inhibit* **platelet aggregation**.
    - *Induce* **vasodilation**.
  - **Thromboxane-A_2 (TXA_2)**;
    - *Induce* **platelet aggregation**.
    - *Induce* **vasoconstriction**.
  - **Leukotrienes (LTs)**;
    - *Powerful* **bronchoconstriction**.
    - *Increase* **vascular permeability**.

- **PGI_2 & PGE_1**; ↓ platelet aggregation & VD
- **PGE_2**; VD, uterine contractions & ↑ platelet aggregation.
- **PGD_2**; inflammatory response, bronchoconstriction & VD.
- **$PGF_{2\alpha}$**; VC, bronchoconstriction & uterine contractions.
- **TXA_2**; ↑ platelet aggregation, VC & bronchoconstriction.
- **LTB_4**; chemotaxis and T-cell proliferation.
- **LTC_4, LTD_4, LTE_4**; VC and bronchoconstriction.

➢ NSAIDs:-

- *These drugs* also *exert* **antipyretic, analgesic** and **anti-inflammatory** *effects*.
- **NSAIDs** are *the most widely* **used medications** *in the world* because of their *efficacy* in *reducing* **pain** and **inflammation**, such as; **osteoarthritis, rheumatoid arthritis, gout, dysmenorrhea, dental pain** and **headache**.
- The **NSAIDs** are *grouped in several* **chemical classes**;

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* Withdrawn from market (some of them may still sold in few countries).

Other Actions

* Ulceration and GI Bleeding *

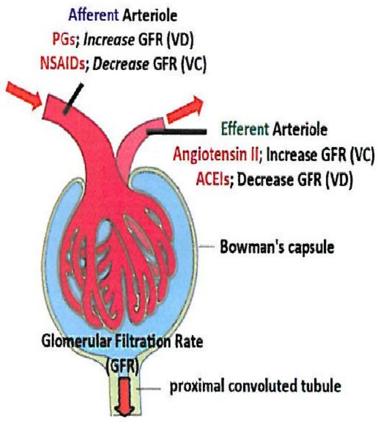
- ***Normally***; **prostaglandins *inhibits* gastric acid *secretion*** (PGI$_2$), and ***stimulate* synthesis** of **protective mucus** in **stomach** and **small intestine** (PGE$_2$ and PGF$_{2\alpha}$).
- **NSAIDs *inhibit* COX-1** ⇨ ***reduce* beneficial *effects*** of **PGs** in the **GIT**, *resulting in* ***increased*** **gastric acid secretion**, ***decrease*** **mucus protection** and ***increased*** **risk** for **GI bleeding** and **ulceration**.
- **Patients** with a ***high*** **risk** for **GI events**, **NSAIDs *should be* used *concomitantly*** with **proton pump inhibitors** or **Misoprostol** (*PGE$_1$ analogue*) to ***prevent*** **NSAID-induced ulcers**.
- **NSAIDs *should be* taken** with **food** or **fluids** to ***diminish*** **GI upset** (*decrease NSAIDs from concentrating in the walls of the stomach*).
- ***Selective* COX-2 *inhibitors***, have ***less effect*** on **GI ulceration** and **bleeding**.

* Antiplatelet Effect *

- ***Normally***; **TXA$_2$ *enhance* platelet aggregation**, *whereas* **PGI$_2$ *decrease* platelet aggregation**.
- **Aspirin** inhibits the synthesis of **TXA$_2$** by ***irreversible acetylation*** of COX enzyme.
- ***Other*** **NSAIDs** also ***inhibit*** **COX *but*** have a ***shorter duration*** **of inhibitory action *because*** they ***cannot*** acetylate COX; that is their action is ***reversible***.
- The ***recommended dose***; ranges from **75-325 mg/d**.
- **Aspirin inhibit platelet function *within* 60 min.**
- ***N.B.***; ***Concomitant administration*** of ***other*** **NSAIDs** can ***diminish*** the **antiplatelet effects** of ***low-dose*** **Aspirin**, ***increase*** the **risk** of **thromboembolic effects** (NSAIDs occupy the active site of COX and prevent aspirin from acetylating COX)
- **Aspirin *not given*** at ***least*** **1 week *before* surgery** (***Antiplatelet effect*** **of Aspirin** *lasts* 8-10 days).

* *Decrease* Renal Blood Flow *

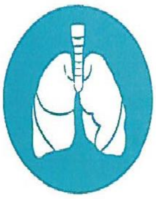
- ***Normally***; **PGE$_2$** and **PGI$_2$**, are responsible for ***maintaining*** **renal blood flow** by ***vasodilation*** in the **kidneys**.
- **NSAIDs *inhibit* COX-1** ⇨ ***reduce*** **beneficial PGs** in the **Kidneys** ⇨ ***decrease*** **renal blood flow** due to ***constriction*** of ***afferent*** **arterioles**.


Afferent Arteriole
PGs; Increase GFR (VD)
NSAIDs; Decrease GFR (VC)
Efferent Arteriole
Angiotensin II; Increase GFR (VC)
ACEIs; Decrease GFR (VD)
Bowman's capsule
Glomerular Filtration Rate
(GFR)
proximal convoluted tubule

- **NSAIDs *decrease*** **sodium** and **water *excretion*** may cause **edema** in ***some patients*** (***patients*** with a ***history of*** **heart failure** or **kidney disease**).
- **NSAIDs** *can* also ***decrease*** the ***beneficial effects*** of **antihypertensive drugs**.
- ***Selective* COX-2 *inhibitors***, have ***less effect*** on renal blood flow.
- **NSAIDs *nephrotoxicity*** can be ***exacerbated*** by **ACEIs** or **ARBs**

- ***Normally***; There is a **balance *between;***
  - **PGI$_2$** (*vasodilator & inhibit platelet aggregation*)
  - **TXA$_2$** (*vasoconstrictor & induce platelet aggregation*).
- **NSAIDs** with a ***very high degree*** of **COX-1 *selectivity*** (such as **Aspirin**); have a **cardiovascular protective effect**, due to ***decrease*** **TXA$_2$ production *mediated by* COX-1**.
- **NSAIDs** with a ***very high degree*** of **COX-2 *selectivity*** (such as **Rofecoxib**), have a ***high risk* for cardiovascular events** (**MI** and **stroke**), due to ***decrease*** **PGI$_2$ production *mediated by* COX-2**.
- **Aspirin** in ***high dose*** (> 325) ***inhibit*** **PGI$_2$ production *mediated by* COX-2** and may carry a ***risk* for CVS events**.

- ***All* NSAIDs** (*non-selective and selective COX-2*) are ***not without*** **CVS risk**.
- **Naproxen** appears to be the ***least*** **CVS risk** (*particularly for patients who require long-term [over a month] use*).



- ***Normally***; There is a **balance *between;***
  - **Cyclooxygenase *pathway*** (Prostanoids formation).
  - **Lipoxygenase *pathway*** (Leukotrienes formation).
- **NSAIDs** cause ***shift*** in **arachidonic acid *from* cyclooxygenase pathway *to* lipoxygenase pathway ⇨ leukotrienes *formation* ⇨ bronchospasm *may occur*** (about 10% of people taking NSAIDs).
- **NSAIDs *should be used with*** **caution** in ***patients with*** **asthma**.
- ***Selective*** **CysLT$_1$ receptor *antagonists*** for **leukotrienes LTC$_4$, LTD$_4$** and **LTE$_4$** such as **Zafirlukast** & **Montelukast** are ***used*** to ***overcome*** **NSAIDs *induced*** **bronchospasm**.

- ***High*** **doses** of **NSAIDs *may cause*** **CNS stimulation** (**confusion, dizziness**) and **tinnitus**.

Therapeutic Uses

NSAIDs *should be* used at the *lowest* effective dose for the *shortest possible* duration of therapy.

A) Anti-inflammatory and **analgesic**: **NSAIDs** are ***used in***;
- ***Treatment of*** **rheumatoid arthritis (RA), osteoarthritis (OA) & gout.**
- ***Mild*** to ***moderate*** **pain *due to*** **multiple causes**; **headache, toothache, backache, menstrual cramps (dysmenorrhea)** and **cold/flu**.
- ***Combinations*** of **NSAIDs** and **Opioids** may be ***effective*** in ***treating severe*** **pain *caused by*** **malignancy**.
- **Ketorolac** can be used for ***severe*** **pain** (analgesic effect of 30 mg of ketorolac = 10 mg of morphine).

B) Antipyretic: **NSAIDs** may be **used to *treat*** **fever**.
- **Aspirin** is ***contraindicated*** in **children** (*under 20 years*) as **antipyretic *with*** **viral infections** such as chickenpox or influenza), due to ***increased*** **risk** for **Reye syndrome** (*see next page*).

C) Cardiovascular:
- ***Low-dose*** **Aspirin** ***used*** in the ***prophylactic treatment*** of **transient cerebral ischemia and thromboembolic stroke**, and ***reduce*** **the incidence of recurrent MI**.

D) Topical:
- **NSAIDs** may be **used topically as anti-inflammatory** and **analgesic**.
- **Salicylic acid** is a ***keratolytic***, **used *topically*** to ***treat*** **corns, calluses** and **warts**.
- **Methyl salicylate** (and **Menthol**) is a **counterirritants, used *topically*** **arthritis and sports rubs.**

Side Effects

- *General* **side effects** for *all* **NSAIDs** (*commonly dose related*)
  - **CNS**: headaches, tinnitus and dizziness.
  - **CVS**: hypertension, fluid retention, edema and risk for CV events.
  - **GIT**: abdominal pain, dysplasia, nausea, vomiting, ulcers or bleeding.
  - **Kidney**: renal insufficiency, renal failure, hyperkalemia & proteinuria.
  - **Lung**: asthma.
  - **Hematologic** (*rare*); thrombocytopenia and aplastic anemia.
  - **Hepatic**: (*rare*) abnormal liver function tests and liver failure.
  - **Skin**: rashes.

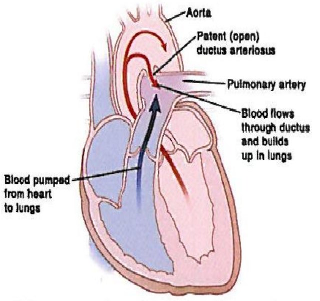
Aspirin Poisoning

- A *single* **overdose Aspirin** or *other* **salicylates** *may cause* ***acute poisoning***. ***Continuous*** **usage** of **Aspirin** or ***other*** **salicylates** and ***elevated*** **dosage** ***over*** **long periods** may cause ***chronic poisoning***.
- **Salicylism** (*mild form* of **salicylates** *toxicity*); is ***characterized by*** **nausea, vomiting,** ***marked*** **hyperventilation, headache, mental confusion, dizziness,** and **tinnitus** (ears ringing).
- ***Severe* salicylate *toxicity***; **Restlessness, delirium, hallucinations, convulsions, coma, respiratory/metabolic acidosis & death** (*respiratory failure*). ***Alkalization*** (**Sodium bicarbonate**) of **blood** and **urine** ***keeps*** **salicylates** *away* ***from*** **brain** and ***enhancing*** **urinary excretion**.

Reye's Syndrome

- **Reye syndrome** or **Reye's syndrome** is a ***rare serious*** **condition** ***characterized by acute*** **encephalopathy** ***and*** **hepatic dysfunction** (*swelling in the liver and brain*).
- **Reye's syndrome** ***typically affects*** **children** and **teenagers** ***after*** a **viral infection** (most commonly the *flu* or *chickenpox*), and is ***associated with*** the ***use of*** **Aspirin** ***during*** the **illness**.
- ***During*** **Reye's syndrome**; **blood sugar level** *typically* ***drops*** while the **blood ammonia level** and **acidity** *rise*.

- ***Most*** **NSAIDs** are **category C** in the ***first*** and ***second*** **trimesters**.
- ***All*** **NSAIDs** ***should not*** (**category D**) be **used** in **third trimester**, may ***increases*** the **risk** of **pulmonary hypertension** in **newborns**, ***due to premature*** **closure of the ductus arteriosus** (**NSAIDs** ***block*** the *synthesis* of **PGE_1** & **PGE_2**, which are ***needed to*** **keep** ***open*** the **ductus arteriosus**).
- ***Persistent*** **opening ductus arteriosus** (**patent ductus arteriosus**) ***after*** **birth** and ***left*** **untreated**; allow poorly oxygenated blood to flow in the wrong direction, weakening the heart muscle and causing complications.
- **NSAIDs** such as **Indomethacin** or **Ibuprofen** (IV) are ***used*** in ***treatment*** of **patent ductus arteriosus (PDA)**.


Aorta
Patent (open) ductus arteriosus
Pulmonary artery
Blood flows through ductus and builds up in lungs
Blood pumped from heart to lungs

- **Alprostadil** is a **PGE_1 analogue**, is ***used to maintaining*** **a patent ductus arteriosus** in **newborns** in certain types of congenital heart disease, until corrective surgery can be carried out.
- ***Low-dose*** **Aspirin** ***may be beneficial*** in **pregnancies** at ***risk for*** the ***development*** of **pregnancy-induced hypertension** and **pre-eclampsia**, and in **fetuses with intra-uterine growth retardation**.
- **NSAIDs** also ***used in management of*** **polyhydramnios** (is a pathological ***increase*** of **amniotic fluid volume** ***in pregnancy*** and is associated with increased perinatal morbidity and mortality).
- **Indomethacin** (IV) is ***one of*** the **tocolytic drugs** ***used to stop*** **uterine contractions** and ***delay*** **labor** (delaying the labor process for 48 hours and up to seven days), via ***inhibition of*** **prostaglandins synthesis**, ***particularly*** **$PGF_{2\alpha}$** and **PGE_2**.

- ***Most*** **NSAIDs** ***displace*** **bilirubin** ***through*** **protein binding** and they are ***contraindicated*** when **breastfeeding** a **neonate** ***with*** **jaundice**.
- The ***American Academy of Pediatrics*** considers **Ibuprofen**, **Indomethacin** and **Naproxen** ***safe*** in **breastfeeding women**.

II) Specific Agents

Salicylates

Diflunisal (Dolobid®)

- **Diflunisal** [dye-FLOO-ni-sal] is a **difluorophenyl** ***analogue*** of **salicylic acid**.
- It is ***used*** in **rheumatoid arthritis** (**RA**), **osteoarthritis** (**OA**) and **muscle pain**.
- **Diflunisal** also had the ***advantage*** of a **twice daily** ***dosage***.
- It ***reported*** causes ***less*** **GIT ulceration** and **tinnitus** *than* **Aspirin**.
- **Diflunisal oral ointment** is a clinically ***useful*** **analgesic** for ***painful*** **oral lesions**.

Salsalate (Disalcid®)

- **Salsalate** [SAL-sa-late] is a ***dimer*** of **salicylic acid**.
- It is ***used*** in **rheumatoid arthritis** (**RA**) and **osteoarthritis** (**OA**).
- ***New studies***; **Salsalate** (3-4.5 gm daily) can ***lower*** **insulin resistance** and ***reduce*** the **levels** of **glucose**, **triglycerides**, and **free fatty acid**. This *inexpensive* **medication** could be a **useful** option in the ***treatment*** of **prediabetes**.

Propionic Acid Derivatives

Ibuprofen (Advil®)	**Dexibuprofen** (Extragesic®)	**Ketoprofen** (Ketofan®)
Dexketoprofen (Dextrafast®)	**Flurbiprofen** (Nalfon®)	**Fenoprofen** (Nalfosab®)
Loxoprofen (Roxogesic®)	**Naproxen** (Aleve®)	**Oxaprozin** (Daypro)

- ***All of these*** **drugs** ***possess*** **anti-inflammatory**, **analgesic** and **antipyretic** ***activity*** and *may be* **used** in ***chronic treatment*** of **rheumatoid** and **osteoarthritis**; because ***their*** **GI side effects** are ***generally less*** **intense** ***than*** that of **Aspirin**.
- **Ibuprofen** [eye-bue-PROE-fen] was ***first*** in this class (***prototype*** of **propionic acid derivatives**), and has the ***lowest risk*** of causing **GI bleeding** (*this advantage is lost at high doses*). It has ***about*** **4 times** the ***analgesic potency*** of **Aspirin**. It is ***available*** in ***multiple*** **formulations**. **Ibuprofen** and **Indomethacin** are ***effective*** in ***closing*** **patent ductus arteriosus** ***in*** **preterm infants**.
- **Dexibuprofen** [dex-eye-bue-PROE-fen] is the ***active*** **dextrorotatory** ***enantiomer*** of **Ibuprofen**.
- **Ketoprofen** [kee-toe-PROE-fen] is a **propionic acid derivative** that ***inhibits both*** **COX** (***higher*** **COX-1 selectivity**) and **LOX** (*lipoxygenase*), ***unlike many*** **NSAIDs**, **inhibits** the ***synthesis*** of **leukotrienes** and **leukocyte migration** into ***inflamed*** **joints** (*in addition to* inhibiting the biosynthesis of prostaglandins), ***less*** **potent** ***than*** **Indomethacin**, ***maximum dose*** is **300 mg/day**.
- **Dexketoprofen** [dex-kee-toe-PROE-fen] is the ***active*** **dextrorotatory** ***enantiomer*** of **Ketoprofen**, it is ***available as*** the **tromethamine salt** (**Dexketoprofen Trometamol**).
- **Flurbiprofen** [flure-BI-proe-fen] is ***available*** in an ***ophthalmic formulation*** for ***inhibition of*** **intraoperative miosis** (Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms), as well as it is also ***orally*** for ***available*** **arthritis**.
- **Fenoprofen** [fen-oh-PROE-fen] and **Loxoprofen** [loxo-PROE-fen]; ***like other*** **NSAIDs** used for ***mild*** to ***moderate*** **pain** and for ***treatment*** of **rheumatoid** and **osteoarthritis**.
- **Naproxen** [na-PROX-en] is a **naphthyl-propionic acid** ***derivative***, It is the ***only*** **NSAID** presently as a ***single*** **enantiomer**, has a ***lowest*** **risk** of **CV events** (*preferred NSAID for people with a high risk of CVS complications; but not without risk*), **Naproxen** ***poses*** an ***intermediate*** risk of **stomach ulcers** ***compared*** to **Ibuprofen** (***double*** that of **Ibuprofen**). It ***may be used alone*** in **menstrual migraine** ***prophylaxis*** or in ***combination*** (**Sumatriptan/Naproxen** Treximet®) in **migraine** ***acute attack***, ***like other*** **NSAIDs** used for ***mild*** to ***moderate*** **pain** & for **rheumatoid**, **osteoarthritis** and **primary dysmenorrhea**. It has been associated with ***pseudoporphyria*** and ***photosensitivity*** in ***some patients***.
- **Oxaprozin** [ox-a-PROE-zin] is a ***unique*** *among the* **propionic acid group** of NSAIDs, ***because*** it has a ***rapid*** **onset of action** and a ***prolonged*** **duration of action** (half-life 50–60 hours). It also has ***mild*** **uricosuric properties** and is ***more useful*** in **gout** ***than*** some ***other*** **NSAIDs**.

Acetic Acid Derivatives

Indomethacin (Indocid®)	**Diclofenac** (Voltaren®)	**Aceclofenac** (Bristaflam®)
Ketorolac (Ketolac®)	**Etodolac** (Etodine®)	**Sulindac** (Clinoril®)
Tolmetin (Rumatol®)	**Nabumetone** (Nabuxan®)	

- **Indomethacin** [in-doe-METH-a-sin] is an **indole** ***derivative***, is a ***very potent non-selective*** **COX inhibitor** (**one of the** ***most potent*** **NSAIDs**), It is also a ***more*** **potent** ***antipyretic*** than *either* **Aspirin** or **Paracetamol**, and it has ***about*** **10 times** the ***analgesic potency*** of **Aspirin** and about ***6 times*** the ***analgesic potency*** of **Ibuprofen**. **Indomethacin** may also ***inhibit*** **phospholipase** A and C, ***reduce*** **neutrophil** ***migration*** and ***decrease*** **T-cell** and **B-cell proliferation**, *so it is* **mainly** ***used for*** acute **gout** *and* **rheumatoid arthritis. Indomethacin** are ***effective*** in *closing* **patent ductus arteriosus** ***in*** **preterm infants**. It has been ***used for*** many other conditions, ***ophthalmic preparation*** is efficacious for **conjunctival inflammation** and to *reduce* **pain** ***after*** **traumatic corneal abrasion**, **Indomethacin** ***oral rinse*** are ***used for*** **gingival inflammation**. **Indomethacin** has ***moderate high*** **risk** of **CV events**, has a ***very high*** **risk** of **GI complications** and ***many*** **CNS side effects**. [**Indomethacin suppositories** ***should be used*** with ***extreme caution*** in **CHILDREN** ***younger than*** **15 year old** (*safety and effectiveness in these children have not been confirmed*).]
- **Diclofenac** [dye-KLOE-fenak] {The name "**Diclofenac**" derives from its chemical name: 2-(2,6-**Dichlo**ranilino) **phenylac**etic acid} is **one** of the ***most potent*** **NSAIDs**, is ***more potent*** **anti-inflammatory** *than* **Indomethacin** and **Naproxen**. **Diclofenac** may also be a ***unique member*** of the **NSAIDs**, it ***inhibits*** the **lipoxygenase pathways** and also may ***inhibit*** **phospholipase A2** with ***higher*** **COX-2 selectivity**, it ***used widely*** in the treatment of **pain** ***associated with*** **renal stone** (*first choice NSAID for renal colic*). It has been ***used for*** ***many*** other conditions, ***very high*** **risk** of **CV events** and ***moderate*** **risk** of **GI complications**. [*Don't waste your time to differentiate between diclofenac sodium and potassium*], [**Diclofenac suppositories** ***should be used*** with ***caution*** in **CHILDREN** ***younger than*** **3 year old** (*safety & effectiveness in these children have not been confirmed*). **Diclofenac** & **Sulindac** cause ***elevation*** of **liver enzymes**, ***increased*** **risk** of **liver toxicity** *compared with* ***other*** **NSAIDs**.
- **Aceclofenac** [a-ce-KLOE-fenak] is the **glycolic acid ester** of **Diclofenac**. The ***incidence*** of **GI complications** of **Aceclofenac** has been reported to be ***significantly lower than*** that of the ***other*** **NSAIDs**, for instance, **2-folds** ***lesser than*** **Naproxen**, **4-folds** ***lesser than*** **Diclofenac**, and **7-folds** ***lesser than*** **Indomethacin**.
- **Ketorolac** [kee-toe-ROLE-ak] is the ***most potent*** and ***most effective*** **NSAID analgesic**, with **efficacy** ***comparable to*** **opioids** (The analgesic effect of 30 mg of **Ketorolac** is similar to 10 mg of **Morphine**), it ***used widely*** in ***short-term treatment*** of ***moderately severe pain*** (*usually after surgery*), due to ***highest incidence*** of **side effects**, **Ketorolac** ***should not use for more than 5 days*** (**oral**, **parenteral** and **intranasal**), the **oral formulation** is ***only*** to be ***used as*** **continuation** to **IV** or **IM therapy**.
- **Etodolac** [ee-toe-DOE-lak] is a ***potent*** **NSAIDs**, The ***anti-inflammatory*** **potency** of **Etodolac** was found to **lie** ***between*** that of **Sulindac** and **Piroxicam** (**Etodolac** was 2.8 times more active than **Sulindac** and 2.2 times ***less active*** than **Piroxicam**). **Etodolac** has a ***low incidence*** of **GI complications**.
- **Sulindac** [sul-IN-dak] is an ***analog*** of **Indomethacin** (***sulfoxide prodrug***), ***developed as*** a ***less*** **toxic**, with ***similar*** **anti-inflammatory** ***potency***, **Sulindac** is ***unique*** **NSAIDs** in ***lesser*** **inhibiting PGs** ***synthesis*** in the **kidneys** (Kidneys can ***deactivate*** the **active metabolite** of **Sulindac** be ***reoxidize*** the **sulfide** to the ***inactive sulfoxide prodrug***) So, it may be ***one*** of the ***safest NSAIDs*** drugs for ***treating*** **osteoarthritis** in ***older people***. Like **Diclofenac**, **Sulindac** may cause ***elevation*** of **liver enzymes**.
- **Tolmetin** [TOLE-met-in] is a **NSAIDs** with a short half-life (1-2 hours) and ***used in*** **osteoarthritis**, **rheumatoid arthritis** & **juvenile rheumatoid arthritis**, with ***mild*** **GI complications** & ***less*** **tinnitus**
- **Nabumetone** [na-BUE-me-tone] is a **non-acidic NSAID**, is a ***prodrug*** which ***contains*** the **non-acidic ketone**, which is ***quickly*** **metabolized to** give the **naphthyl-acetic acid derivative** (it was designed to ***decrease*** some of the **GI problems** normally associated with the acidic functionality of these agents), ***long*** **half-life** (*more than 24 hours*), is a ***more potent inhibitor*** of **COX-2**, is ***very similar*** to **other NSAIDs**, with ***less*** **GI complications** and ***less*** **risk** of **CV events** (Effects of **Nabumetone** on blood pressure control in hypertensive patients on ACE inhibitors is also good).

Enolic Acid Derivatives (Oxicams)

Piroxicam (Feldene®)	**Tenoxicam** (Epicotil®)	**Lornoxicam** (Xefo®)
Meloxicam (Mobic®)	**Droxicam**	

- **Piroxicam** [peer-OX-i-kam] is an **oxicam** (***nonselective COX inhibitor***), at ***high concentrations*** also ***inhibits*** **polymorphonuclear leukocyte migration**, ***decreases*** **oxygen radical production**, and ***inhibits*** **lymphocyte function**. Its ***long*** **half-life** (*once-daily*), ***very high*** **risk** of **GI complications**.
- **Tenoxicam** [ten-OX-i-kam] is an **oxicam**, there is ***no significant difference*** between **Tenoxicam** and **Piroxicam** (*some studies found* **Tenoxicam** ***more*** **effective** and ***better*** **tolerated** than **Piroxicam**).
- **Lornoxicam** [lorn-OX-i-kam] is ***unique*** *among the* **enolic acid derivatives** of **NSAIDs** in that it has a ***rapid onset*** of **action** and a *relatively* ***short*** **half-life** (3-4 hours).
- **Meloxicam** [mel-OX-i-kam] has a ***higher*** **COX-2 selectivity** (it was initially introduced as a selective COX-2 inhibitor), it has a ***fewer*** **risk** of **GI complications** with ***high moderate*** **risk** of **CV events**. It is ***available in*** **7.5mg** and **15mg doses**. ***October, 2015***; FDA approved a ***new formulation*** of **Meloxicam** (Vivlodex®) contains ***microparticles*** of **Meloxicam** (using Solu-Matrix Fine Particle Technology) to ***reduce*** **dose** (5mg and 10mg) and ***decrease*** **toxicity** for the ***treatment of*** **osteoarthritis**.
- **Droxicam** [dr-OX-i-kam] is a ***prodrug*** of **Piroxicam**.
- ***Long-term use*** of **Oxicams** and **Ketorolac** is ***associated with*** an ***increased*** **risk** of **chronic kidney disease**.

Fenamic Acid Derivatives

Mefenamic Acid (Ponstan®)	**Meclofenamic Acid** (Meclomen®)
Tolfenamic Acid (Fastgraine®)	**Flufenamic Acid**

- **Mefenamic** [me-fe-NAM-ik] **acid** is a ***non-selective*** **COX inhibitors** (**COX-2 >> COX-1**) and also ***may act as*** **prostaglandins receptor** ***antagonist***, these effects may also be ***responsible for*** its ***effectiveness*** in the ***treatment of*** **primary dysmenorrhoea**. **Mefenamic acid** is also ***used in*** **osteoarthritis** and **rheumatoid arthritis**.
- **Meclofenamate** [me-kloe-fen-AM-ate] or **Meclofenamic acid** as **Mefenamic acid** ***used for*** treatment of **dysmenorrhoea**, **osteoarthritis** and **rheumatoid arthritis**.
- **Tolfenamic** [tol-fe-NAM-ik] **acid** is ***used to*** treat **migraines** and **severe headaches**, It is available in some countries for humans and for animals.
- **Flufenamic** [flu-fe-NAM-ik] **acid** is also available in some countries.

Other Agents

Nimesulide (Sulide®)

- **Nimesulide** is a ***sulfonanilide derivatives***, is a ***relatively*** **COX-2** ***selective***, it has ***analgesic***, ***antipyretic*** and **anti-inflammatory effects**.
- It has ***low incidence*** of **GI complications**.
- It ***primary used*** as ***short term*** in the ***treatment*** of ***acute*** **pain**, and ***primary*** **dysmenorrhea**.
- **Nimesulide** ***should not*** be ***taken*** as **long-term**, (*like* **arthritis**), ***due to*** its ***association with*** an ***increased risk*** of **liver toxicity**.
- ***Due to risk*** of **hepatotoxicity**, **Nimesulide** has been ***withdrawn from*** **market** in ***several*** **countries**.

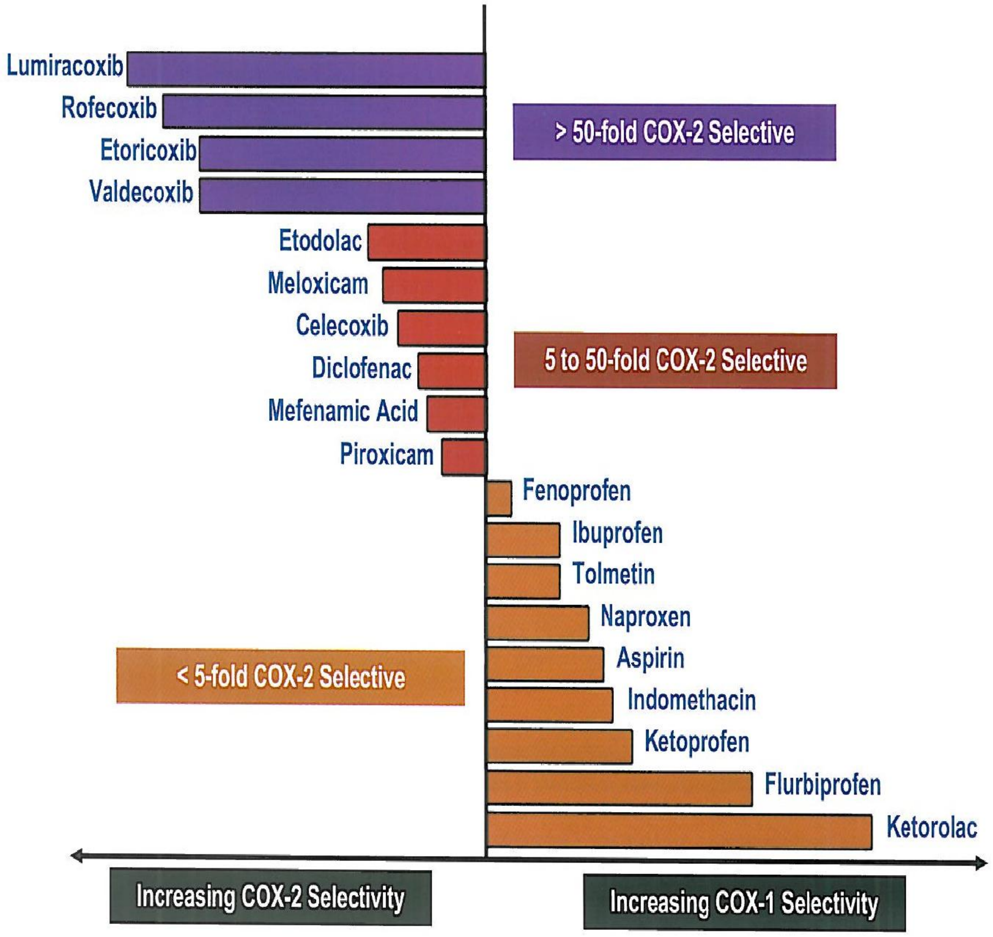
Metamizole (Dipyrone) (Novalgin®)

- **Metamizole** (**Dipyrone**) is a ***non-opioid analgesic drug***.
- **Metamizole** is an ***ampyrone sulfonate*** (***pyrazolone derivatives***) ***analgesic***, ***antispasmodic*** and ***antipyretic***. ***Like*** **Paracetamol**, it has ***minimal*** **anti-inflammatory effects**, this agent is ***still*** **incorrectly** ***classified as*** a **NSAID**.
- It was ***first used*** in1922 (Novalgin®) and for ***many years*** it was available **OTC** in ***most countries***, ***until several*** **reported cases** of **agranulocytosis**, *but it is still available OTC in some countries*.

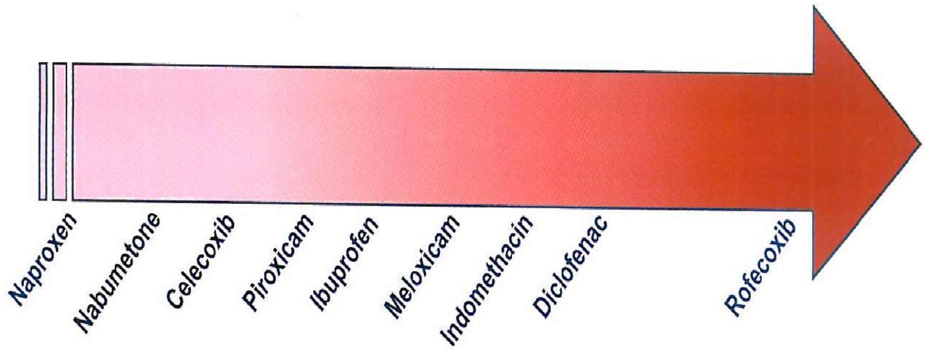
Selective COX-2 Inhibitors (Coxibs)	
Celecoxib (Celebrex®)	**Rofecoxib** (Vioxx®)
Valdecoxib (Bextra®)	**Parecoxib** (Dynastat®)
Etoricoxib (Arcoxia®)	**Lumiracoxib** (Prexige®)

- **Celecoxib** [sel-e-KOX-ib] is a ***reversible selective*** **COX-2 inhibitor** (about 10–20 times more selective for COX-2 than for COX-1). Celebrex® was one of Pfizer's ***best-selling drugs***.
- **Celecoxib** is ***approved for*** the treatment of **rheumatoid arthritis**, **osteoarthritis**, and ***acute mild*** to ***moderate*** **pain** (has similar efficacy to NSAIDs in the treatment of pain).
- **Celecoxib** is ***associated with less*** **GI complications** ***than*** **other NSAIDs**. ***Like other NSAIDs***, it has a ***similar*** **risk** of **CV events**, it has a **sulfonamide** ***structure*** (***contraindicated*** for ***patients*** with **sulfa** allergy). **Celecoxib** ***metabolism*** is ***primarily by*** **CYP2C9**, **Fluconazole** and **Fluvastatin**, may ***increase*** serum levels of **Celecoxib**.
- **Rofecoxib**; **Merck & Co.** ***withdrew*** **Vioxx®** from market **voluntarily**, due to an ***increased*** **risk** of **CV events**; **heart attack** and **stroke** (**Rofecoxib** inhibits COX-2 80 times more than the COX-1).
- **Valdecoxib**; **Pfizer** ***withdrew*** **Bextra®** from the US market on recommendation **by the FDA** due to an ***increased*** **risk** of **CV events**.
- **Parecoxib** is a ***water-soluble*** and ***injectable prodrug*** of **Valdecoxib**, It is marketed in the European Union.
- **Etoricoxib** is ***approved in some countries*** (*not in the US*) by **Merck & Co.**
- **Lumiracoxib** is still sold in ***few countries*** by **Novartis**.

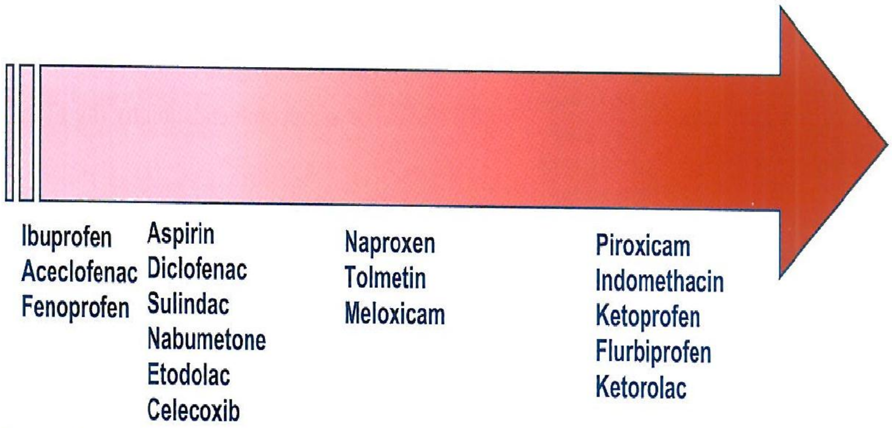
➢ Relative selectivity of some commonly used NSAIDs:-



➢ Relative risk for CV events of some commonly used NSAIDs:-



➢ Relative risk for GI complications of some commonly used NSAIDs:-



➢ Special Populations:-

NSAIDs should be used at the lowest effective dose for the shortest possible duration of therapy

Population or Disease State	Preferred Agents
- Pregnancy	- 1st, 2nd trimesters; *Most* NSAIDs are Category C - 3rd trimesters; *All* NSAIDs are Category D
- Patent Ductus Arteriosus (PDA)	- Indomethacin or Ibuprofen.
- Primary Dysmenorrhoea	- Mefenamic acid, Ibuprofen and Naproxen. - *Other* NSAIDs are *effective*.
- High CV Risk (Coronary Diseases)	- *All* NSAIDs are *should be avoided*. - *If must be used*, Naproxen appears to be the *least* CVS risk.
- High GI Risk (ulcers or bleeding)	- *All* NSAIDs are *should be avoided*. - *If must be used*, Ibuprofen and Celecoxib appears to be the *least* GI risk and used as co-therapy with Misoprostol or *proton pump inhibitors* (e.g. Omeprazole).
- Asthma and COPD	- NSAIDs can *prescribed to* patients with asthma who *have no previous* history of NSAID-associated symptoms. - *About* 8-20% of adult asthmatics *experience* bronchospasm *following ingestion* of NSAIDs. - People who *have had* a *hypersensitivity reaction* to a NSAID *should avoid all* NSAIDs.
- Renal Diseases	- *All* NSAIDs are *should be avoided* in *people* with CKD. - *If must be used*, Sulindac, Aspirin and Ibuprofen appears to be the *least* nephrotoxic risk.
- Renal Stone (Renal Colic)	- Diclofenac (*strongest in effectiveness in renal* colic).
- Children	- Ibuprofen is the *most appropriate* NSAID *for* children.

- COX-Inhibiting Nitric Oxide Donators (CINODs); Are a new class of non-steroidal anti-inflammatory drug (NSAID) with a nitric oxide (NO)-donating moiety by improving vascular safety, most likely via vasodilatation such as Naproxcinod (NO-naproxen).

Other Analgesics

Paracetamol or Acetaminophen (Panadol®) (Tylenol®) (Calpol®)

- **Acetaminophen** [a-SEET-a-MIN-oh-fen] is the name **generally *used in*** the **US** and **Japan**, **Paracetamol** is used in ***internationally***.
  - ***Both*** *come from* a **chemical name**;
    - Para-**acetyl****aminophen**ol; **Acetaminophen**.
    - **Para-acetyl**aminophenol; **Paracetamol**.
  - **Tylenol®** is an ***American*** **brand** of **Acetaminophen**, is ***derived from*** the chemical name;
    - N-ace**tyl**-para-aminoph**enol** (APAP) (or para-acetylaminophenol); **Tylenol®**.
  - **Panadol®** is one of GlaxoSmithKline's (GSK) trade names for **Paracetamol**.
  - **Calpol®** is a brand of **Paracetamol** children's medicine sold in the UK, and other countries.
- **Phenacetin** is a ***prodrug*** that is ***metabolized to*** **Paracetamol**, is ***more toxic*** than its **active metabolite**, it ***has no significant*** **anti-inflammatory *effects***, so it is ***not*** **considered** an **NSAID**.

History

- In 1886; **Acetanilide** was the first ***aniline derivative*** used as analgesic and antipyretic, but its unacceptable toxic effects (methemoglobinemia).
- In 1887; **Phenacetin** (another aniline derivative) was introduced by Bayer, and was used as an analgesic and antipyretic, but it have been shown in an animal model to have carcinogenesis.
- **Paracetamol** is the active metabolite of **Acetanilide** and **Phenacetin**.
- In 1947; strong evidence that **Paracetamol** did not cause methemoglobinemia, this led to a "rediscovery" of **Paracetamol**.
- In 1950; **Paracetamol** was first marketed in the US under the name Triagesic®, a combination of **Paracetamol**, **Aspirin**, and **Caffeine**, in 1951 of three users stricken with the blood disease agranulocytosis led to its removal from market. After years it became clear that the disease was unconnected with **Paracetamol**.
- In 1953; **Paracetamol** was marketed under the name Panadol® (by Sterling-Winthrop Co), available only by prescription, and promoted as preferable to **Aspirin** since it was safe for children and people with ulcers.
- In 1955, **Paracetamol** (Panadol®) was introduced to hospitals in the United Kingdom, it was advertised as being "gentle on the stomach",
- In 1983, Sterling introduced Panadol® to the United States market.
- The concerns about Paracetamol's safety delayed its widespread acceptance until the 1970s.
- In 1994; Sterling Winthrop was sold Panadol® rights to SmithKline Beecham.
- ***Now*** **Paracetamol** is widely viewed as cheap, safe and effective, is a widely used drug for the treatment of pain and the reduction of fever (antipyretic).

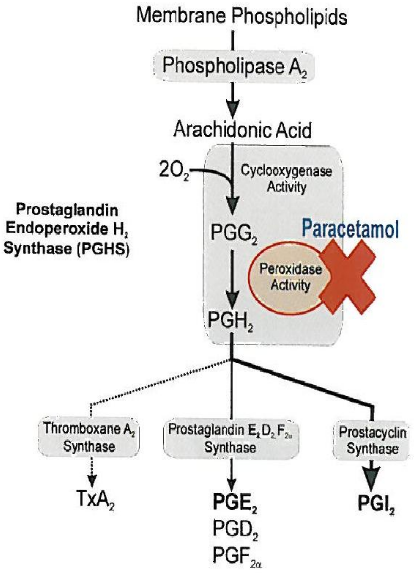
Pharmaco Kinetics

- *Administration*; It is ***typically by*** **oral route *but*** is ***also available*** **rectally** and **intravenously** (perfalgan®).
- *Absorption*; it is ***rapidly absorbed*** by the **GIT**, **absorption** is ***related to*** **gastric emptying rate** (**Metoclopramide** ⇨ ***increase*** **gastric emptying rate** ⇨ ***increase*** **Paracetamol absorption**). ***Plasma peak concentration***; **30-60 minutes**.
- *Distribution*; ***rapidly*** throughout ***most*** **tissues** and **fluids**, ***slightly*** **bound** to **plasma proteins**.
- *Metabolism*; ***extensively*** metabolized (*predominantly* in the **liver**).
  - The ***major*** **metabolites** being the **sulphate** and **glucuronide conjugates** (*inactive*).
  - A ***minor*** **fraction** of **Paracetamol** is ***converted to*** a ***highly reactive*** **alkylating metabolite** (**N-acetyl-p-benzoquinone** or **NAPQI**) by **CYP450**, **NAPQI** reacts ***irreversibly*** with the **sulfhydryl (S-H) group** of **glutathione** in the liver, ***forming*** a **nontoxic substance** (Large doses of **Paracetamol** cause acute hepatic necrosis as a result of depletion of glutathione and excess of NAPQI), (This damage can be prevented by the early administration of sulfhydryl compounds such as **Methionine** and **N-acetylcysteine**).
- *Excretion*; ***All products*** are excreted by the **kidneys**.

Mechanism OF Action

- **After** ***more than*** **100 years,** the ***exact*** **mechanism** of **Paracetamol** is ***still*** **unclear**.
- There is ***evidence*** for a number of **central mechanisms**; including ***effects*** on **prostaglandin** ***production***, and on **serotonergic** and **cannabinoid** ***pathways***.

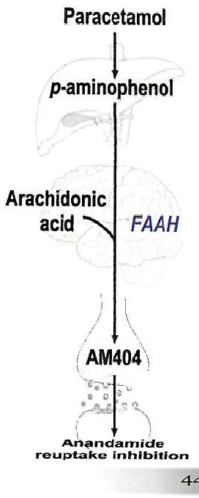
1) ***Prostaglandin inhibition***;


Membrane Phospholipids
Phospholipase A2
Arachidonic Acid
2O2
Cyclooxygenase Activity
Prostaglandin Endoperoxide H2 Synthase (PGHS)
PGG2
Paracetamol
Peroxidase Activity
PGH2
Thromboxane A2 Synthase
Prostaglandin E2 D2 F2α Synthase
Prostacyclin Synthase
TxA2
PGE2
PGD2
PGF2α
PGI2

- The ***cyclic pathway*** is ***initiated*** through the action of **prostaglandin G/H synthase** (*also called* **prostaglandin-endoperoxide synthase; PGHS**).
- ***This enzyme*** possesses ***two*** **active sites: cyclooxygenase (COX)** and **peroxidase (POX)**.
- ***Conversion*** of **arachidonic acid** to **prostanoids**, by **two-stages**;
  1) **COX site**; ***produce unstable intermediate*** **hydroperoxide, prostaglandin** G_2 **(**PGG_2**)**.
  2) **POX site**; ***convert*** **prostaglandin** G_2 ***to*** **prostaglandin** H_2.
- **Paracetamol** ***interferes indirectly*** by ***acting as*** a ***reducing*** **co-substrate** at the **POX site**.
- ***In normal cells*** (**brain**); ***concentration*** of **arachidonic acid** is ***low***, **Paracetamol** is a ***potent inhibitor*** of **PG synthesis**.
- **In broken cells** (**inflammation**); ***concentration*** of **hydroperoxides** is ***high***, **Paracetamol** is ***weakly inhibit*** **PG synthesis**.
- ***This theory*** **explains** the ***differential activity*** of **Paracetamol** in the **brain** (peroxide concentrations are low), vs peripheral sites of inflammation (high peroxide levels).
- ***Another suggestion*** (weak); **Paracetamol** may ***inhibit*** **COX-3 isozyme** (*discovered in 2002*), was thought to be ***found active*** in the **CNS**, rather than at the ***site of*** **inflammation** in ***peripheral***.

2) ***Serotoninergic pathway activation***; ***Serotonergic pathways*** are ***part*** of the **pain system**. It has been demonstrated that, the **analgesic** ***effects*** of **Paracetamol** can be ***partially inhibited*** by **co-administration** of **5-HT3-receptor** ***antagonists*** (**Ondansetron**).

3) ***Endocannabinoid enhancement***;


Paracetamol
p-aminophenol
Arachidonic acid
FAAH
AM404
Anandamide reuptake inhibition

- *In the presence of* **fatty acid amide hydrolase (FAAH)** ***enzyme*** in the **CNS**; **Paracetamol** (via an *intermediary*, **p-aminophenol**, *formed in the liver*) is ***conjugated with*** **arachidonic acid** to form the ***active metabolite***, **N-arachidonoylphenolamine (AM404)**.
- **AM404** ***inhibits*** the **reuptake** of the **endocannabinoid** (**Anandamide**), ***from*** **synaptic clefts**, ***increasing*** **cannabinoid receptor activation** on the ***post-synaptic*** **membrane**.
- This would ***explain*** the **experiences** of **relaxation, tranquility,** and **euphoria** *reported by many* **Paracetamol** *users*.

- **Paracetamol** is an **analgesic/antipyretic** ***of choice*** for;
    - **Children**, with viral infections or chickenpox (due to the risk of Reye syndrome with aspirin).
    - **Pregnancy** and **breastfeeding women**.
        - Some study provides evidence that is a link between **Paracetamol** exposure in pregnancy and infant and development of childhood asthma; 3 to 7 years old).
        - Some study provides evidence that is a link between Paracetamol exposure in pregnancy & development of childhood ADHD or autism.
    - ***Patients with*** **CV risk** or **GI complications**.
    - **Asthmatic patients**.

Therapeutic Uses

- *Therapeutic Uses*;
    - **Fever**; **Paracetamol** is used for ***reducing*** **fever** in **people** of ***all*** **ages**.
        - Current guidelines of the WHO, which recommend that **Paracetamol** should be reserved for children with a high fever (38.5C or above).
    - **Pain**; **Paracetamol** is ***used for*** the relief of ***mild to moderate pain***.
        - **Paracetamol** is recommended by the American College of Physicians and the American Pain Society as a first-line treatment for low back pain. Recent study provides evidence that is **Paracetamol** is ineffective in the treatment of low back pain
        - **Paracetamol** in combination with NSAIDs, may be more effective for treating postoperative pain.
    - **Headaches**; **Paracetamol** in ***combination with*** **Caffeine** is ***highly effective*** in treatment of **tension** or **migraine headache**.
        - **Caffeine** ***accelerates*** **absorption** and ***enhances*** the **analgesic effect** of **Paracetamol**.
    - **Osteoarthritis**; In 2012 the American College of Rheumatology ***recommends*** **Paracetamol** with ***other*** **several options** for ***people with*** **osteoarthritis**.
        - ***In 2016***; a large-scale analysis; researchers found that **Paracetamol** does not meet the minimum standard of clinical effectiveness in reducing pain or improving physical function in patients with knee and hip osteoarthritis.
- ***Novel uses***; 1 g IV Paracetamol before induction of anaesthesia, was found to be equally successful to ketamine in preventing opioid (**Remifentanil**) Induced hyperalgesia (is an increased sensitivity to pain).

Dose

- *Medicines and Healthcare products Regulatory Agency (MHRA) guidelines for* **IV** ***Paracetamol*** *dosing (most accurate and updated)*;

Weighing	Dose per administration	Max. daily dose
< 10 kg	7.5 mg/kg	30 mg/kg
10-33 kg	15 mg/kg	60 mg/kg (max. 2gm)
33-50 kg	15 mg/kg	60 mg/kg (max. 3gm)
>50 kg	1 gm	4 gm

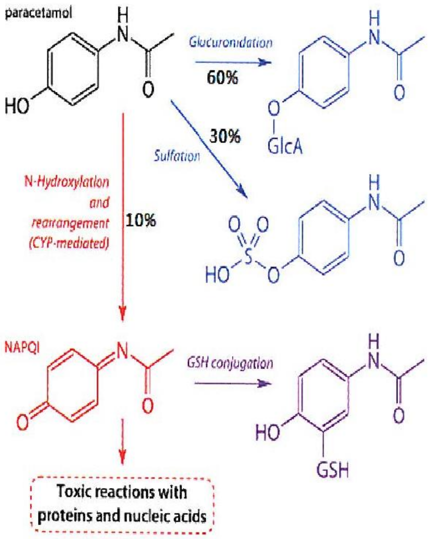
- *N.B*;
    - ***Maximum single adult dose***: **1 gm** (oral or IV).
    - ***Minimum dosing interval***: ***every*** **4 hours**.
    - ***Acute ingestion*** of **15 g** of **Paracetamol** ***may be*** **fatal**, **death** being ***caused by severe*** **hepatotoxicity**, *sometimes associated with* **acute renal tubular necrosis**.
- *Toxic Dose*; *Acute ingestion*; > 150-200 mg/kg in children or 7 g in adult is considered potentially toxic.
- ***Severe renal impairment*** (CrCl less than 30 mL/min); ***Longer*** **dosing intervals** and a ***reduced*** **total daily dose**.
- ***Severe hepatic impairment***; **Paracetamol** is ***contraindicated***.
- ***Mild*** to ***moderate*** **hepatic impairment**: ***Used with*** **caution** (***reduce*** **total daily dose** and/or ***used in combination with*** **glutathione analogues** such as; **Methionine** (is an essential amino acid which serves as a precursor for the amino acid **Cysteine** which will be incorporated in glutathione "GSH" synthesis.

- *At normal therapeutic doses*, **Paracetamol** is *virtually free* of ***significant*** **side effects**. *With large doses*; **Hepatic necrosis** (a *very serious* and *potentially* **life-threatening condition**) *may occur*.

☞ *Metabolism in therapeutic dose*;

- *About 60%* of **Paracetamol** by **glucuronidation** and ***about 30%*** by **sulfonation** ⇨ to *inactive* **products**.
- *About 10%* by **cytochrome P450** (CYP3A4 and CYP2E1) ⇨ to **alkylating metabolite** ***known as*** **NAPQI** (N-acetyl-p-benzoquinone imine) ⇨ ***Highly toxic*** ***but*** ***rabidly*** **detoxified** by ***irreversibly conjugated*** with the **sulfhydryl groups** of **glutathione**.

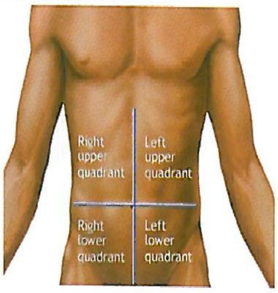
Toxicity


paracetamol
Glucuronidation
60%
GlcA
30%
Sulfation
N-Hydroxylation and rearrangement (CYP-mediated)
10%
NAPQI
GSH conjugation
GSH
Toxic reactions with proteins and nucleic acids

☞ *Metabolism in toxic dose*;

- ***High dose*** of **Paracetamol** cause ⇨ *saturation* of **glucuronidation** ⇨ ***shunting metabolism*** to **cytochrome** ⇨ ***increase amount*** of **NAPQI** ⇨ **glutathione system** ***not able*** to **detoxify NAPQI** ***due to depletion*** of **–SH group** ⇨ **Acute hepatic necrosis**.

- *Clinical manifestation during toxicity*;
  - **Phase I** (during 24 hours after ingestion);
    - **Nausea, vomiting** and ***may be*** **asymptomatic**.
    - *Normal* **hepatic transaminases ALT** and **AST**.
  - **Phase II** (24-72 hours after ingestion);
    - Signs of ***liver damage*** are ***increased*** e.g. **right upper quadrant pain**.
    - *Mild* **increase** in **ALT** and **AST**.
  - **Phase III** (3-4 days after ingestion);
    - ***Symptoms of*** **hepatic necrosis**; **hepatic encephalopathy**, **jaundice**, **coagulopathy** and **hypoglycemia**.
    - **Acute renal failure** ***may*** **develops**.
    - **Death** ***may occur*** from **multiorgan** ***failure***.
  - **Phase IV** (3-4 weeks) (**recovery phase**):
    - **Clinical recovery** may take up to **21 days**; however, ***complete*** **hepatic histologic** ***recovery*** requires ***several*** **months**.


Right upper quadrant
Left upper quadrant
Right lower quadrant
Left lower quadrant

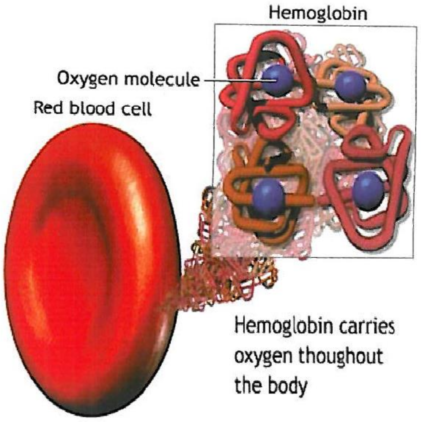
- **N-acetylcysteine (NAC)** is ***nearly*** **100% hepatoprotective** ***within*** **8 h.** ***after*** an ***acute*** **Paracetamol ingestion**;
  - **Oral NAC**; ***loading dose*** of 140 mg/kg, ***followed by*** 70 mg/kg, every 4 hours for 17 doses.
  - **IV NAC**; - ***loading dose***: 150 mg/kg IV in 200 mL of 5% dextrose and infuse over 1 h.
    - ***Dose 2***: 50 mg/kg IV in 500 mL 5% dextrose over 4 h.
    - ***Dose 3***: 100 mg/kg IV in 1000 mL 5% dextrose over 16 h.

Propacetamol is a ***prodrug*** form of **Paracetamol** used IV, **2g** of **Propacetamol** are ***equivalent to*** **1g** of **Paracetamol**.
Benorilate or **Benorylate**, is an ester-linked ***co-drug*** of **Aspirin** with **Paracetamol**.

Anemia

➢ Overview:-

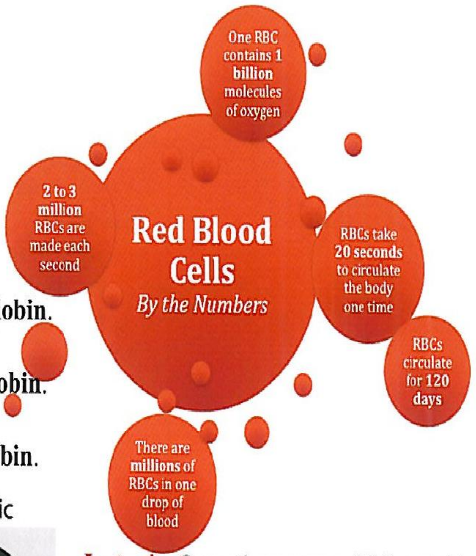
- ***Definitions***:
  - **Anemia** (or **Anaemia**), is a ***decrease*** in the ***amount*** of **red blood cells (RBCs)** or **hemoglobin** ***in the blood***.
  - It can also be ***defined as*** a ***lowered ability*** of the **RBCs** to ***carry adequate*** **oxygen** ***to the*** **body's tissues**.
  - It is usually ***defined clinically*** as a ***reduction*** of the **hemoglobin concentration** to ***less than*** 130 g/L (**13 g/dL**) in **males** or ***less than*** 120 g/L (**12 g/dL**) in **females**.

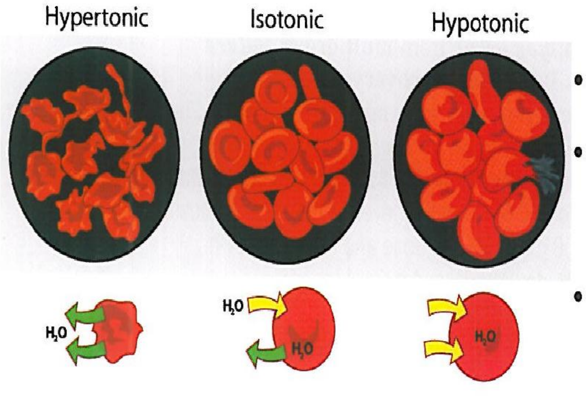

Hemoglobin
Oxygen molecule
Red blood cell
Hemoglobin carries oxygen thoughout the body

- The word **anaemia** is ***from*** **Greek**, meaning **without blood** (**an=without**, **heam =blood**).
- **Anemia**, ***like a*** **fever**, is a ***sign*** that ***requires*** **investigation** to ***determine*** the ***underlying*** **causes**.
- ***Prevalence***: **Anemia** is the ***most common*** **blood disorder**.
  - **In 1985**, the WHO estimated that about **30%** of the ***world*** **population** was **anemic**.
  - **In 1992**, the WHO estimated that **37%** of ***all*** **women** were **anemic**.
  - **In 2008**, the WHO estimated ***globally***, anaemia affects **1.62 billion people**, which corresponds to **24.8%** of the **population**. The highest prevalence is in preschool-age children (47.4%), and the lowest prevalence is in men (12.7%).
  - **In 2013**, **iron deficiency anemia** resulted in about **183,000 deaths**, down from **213,000** deaths in 1990.

➢ Morphology/Terminology:-

- **Normocytic cells**;
  - ***Normal*** **size of RBCs**.
- **Macrocytic cells**;
  - ***Larger*** **size of RBCs**.
- **Microcytic cells**;
  - ***Smaller*** **size of RBCs**.
- **Normochromic cells**;
  - ***Normal*** **concentration of hemoglobin**.
- **Hyperchromic cells**;
  - ***Higher*** **concentration of hemoglobin**.
- **Hypochromic cells**;
  - ***Lower*** **concentration of hemoglobin**.

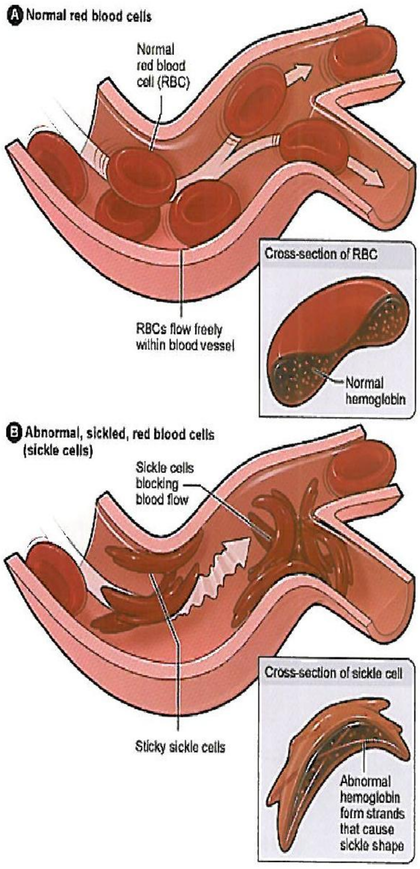

One RBC contains 1 billion molecules of oxygen
2 to 3 million RBCs are made each second
Red Blood Cells
By the Numbers
RBCs take 20 seconds to circulate the body one time
RBCs circulate for 120 days
There are millions of RBCs in one drop of blood


Hypertonic
Isotonic
Hypotonic
H₂O
H₂O
H₂O
H₂O
H₂O

- **Isotonic**; Osmotic pressure (OP) ***outside*** the RBCs = OP ***inside*** the RBCs.
- **Hypertonic**; OP ***outside*** the RBC > OP ***inside*** the RBCs. The water inside RBCs exits to equalize OP, causing the cells to **shrink**.
- **Hypotonic**; OP ***outside*** the RBC < OP ***inside*** the RBCs. The cells take water to equalize the OP, causing them to **swell** and potentially **burst**.

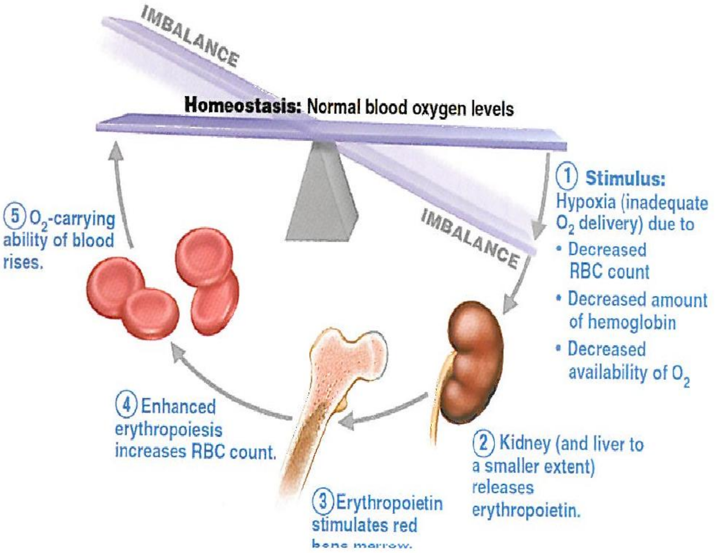
➢ Red Blood Cells (RBCs):-

- **Red blood cells** or **red blood corpuscles** (**RBCs**); *also called* **erythrocytes**, are *responsible for* ***delivering*** **oxygen** to the **body tissues.**
- **RBCs** are ***rich*** in **hemoglobin**, an ***iron-containing*** **biomolecule** that can ***bind*** **oxygen.**
- *Structure*; ***mature red blood cells***; are **flexible** and **oval biconcave disks**, they ***lack*** a **cell nucleus** and **most organelles** (to accommodate maximum space for hemoglobin).
- **RBCs** ***develop*** in the **bone marrow** and **circulate for** *about* **100-120 days.**
- *Approximately* **40-45%** of the **blood's volume** is **red blood cells.**
- *Approximately* **5 million RBCs** ***per*** **one blood drop.**
- ***Approximately*** **270 million** of **hemoglobin** ***per*** **one red blood cell.**
- *Approximately* **2.4 million** ***new*** **RBCs** are *produced* ***per*** **second** in **human adults.**
- ***Each*** **circulation** *takes about* **20 seconds.**
- The **red blood cells** in *adult human male* store about **2.5 grams** of **iron** (about 65% of the total iron in the body).



A Normal red blood cells
Normal red blood cell (RBC)
RBCs flow freely within blood vessel
Cross-section of RBC
Normal hemoglobin
B Abnormal, sickled, red blood cells (sickle cells)
Sickle cells blocking blood flow
Sticky sickle cells
Cross-section of sickle cell
Abnormal hemoglobin form strands that cause sickle shape

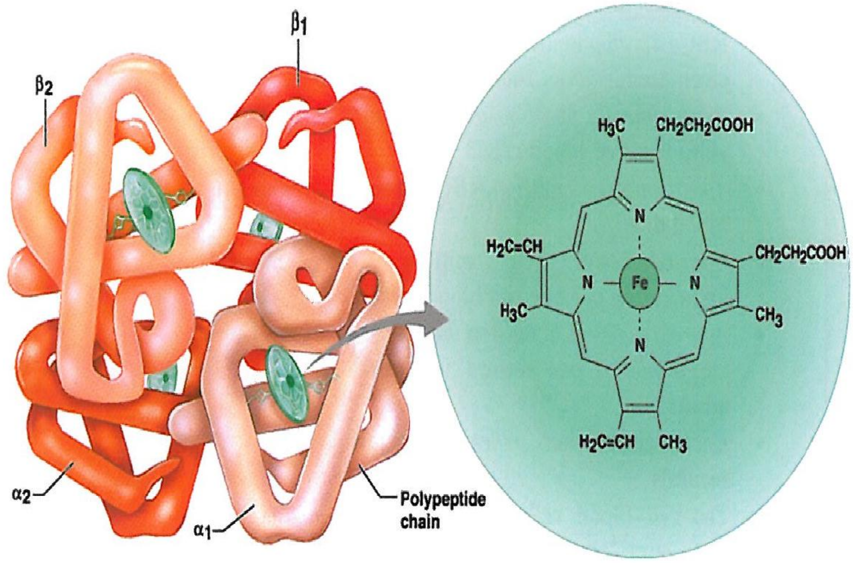
- Formation of RBCs (*Erythropoiesis*);
    - ***Erythropoiesis***; from Greek '***erythro***' *meaning* "***red***" and '***poiesis***' meaning "***to make***" is the process which ***produces*** **RBCs** (**erythrocytes**).
    - **Kidneys** respond to a ***lower*** **oxygen concentration** in the **blood**, which then ***secrete*** the hormone **Erythropoietin.**
    - **Erythropoietin** ***travels to*** the **bone marrow** and ***stimulates*** the **production** of **RBCs.**
    - ***Damaged*** or ***old*** **RBCs** are ***destroyed*** *primarily* by the **spleen.**



IMBALANCE
Homeostasis: Normal blood oxygen levels
IMBALANCE
① Stimulus: Hypoxia (inadequate O_2 delivery) due to
• Decreased RBC count
• Decreased amount of hemoglobin
• Decreased availability of O_2
② Kidney (and liver to a smaller extent) releases erythropoietin.
③ Erythropoietin stimulates red
④ Enhanced erythropoiesis increases RBC count.
⑤ O_2-carrying ability of blood rises.

➢ Hemoglobin:-

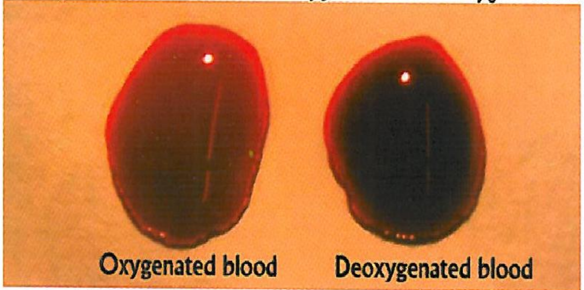
- **Hemoglobin** or **haemoglobin** (**Hb** or **Hgb**); is the ***iron-containing*** **oxygen-transport metalloprotein** in the **red blood cells**.
- **Structure**: **hemoglobin** has **two parts**; **heme** (**prosthetic group**) and **goblin** (**Protein**).
  - **Heme**: consists of an **iron** in the *forum of* **ferrous** (Fe^{2+}) held in a **heterocyclic ring**, *known as* a **porphyrin**. This **porphyrin ring** *consists of* ***four*** **pyrrole molecules** linked together (by *methine bridges*) with the **iron ion** bound in the **center**. The **iron ion**, which is the ***site*** of **oxygen binding**.
  - **Globin**: is the protein part and consist of ***four*** **chains**.



(a) Hemoglobin **(b) Iron-containing heme group**

- ***Main*** **Functions**;
  - **Oxygen carrier**; the ***main function*** of **hemoglobin** is **carry oxygen** *from* **lungs** *to* **all tissues.** In the lung, hemoglobin is contact with oxygen to form oxy-hemoglobin, by week bond. When blood reaches to tissues, bond is broken and oxygen is diffused.

    Oxygen + Hemoglobin ⇌ Oxy-hemoglobin
  - **Carbon dioxide carrier**; ***some*** (about 20–25% of the total) of **carbon dioxide** is ***transported from*** **tissues** ***to*** **lungs** through hemoglobin as carbaminohemoglobin (the majority of carbon dioxide transported via plasma).
  - **Color of blood**; the blood's **red color** is ***due to*** the **spectral properties** of the **hemic iron ions in hemoglobin**. When **RBCs** are ***separated from*** the **blood**, the **red color** ***disappears***. **Oxygenated blood** in **arteries** and **capillary** are **bright red** (oxygen imparts a strong red color to the heme group). **Deoxygenated blood** in **veins** are **drake red** (*the spectrum of light absorbed by hemoglobin differs between the oxygenated and deoxygenated states*).



  - **Buffering action**; Hemoglobin also acts as a buffer, to resist change in blood pH.
  - **Erythrocyte metabolism**; Hemoglobin plays an important role in the modulation of erythrocyte metabolism.
  - **Interaction with drugs**; Not only for oxygen, but hemoglobin act a very important role the transport of various drugs to their site of action.

- **Normal Types of Hemoglobin**; there are **seven types** of **haemoglobin** throughout a human's life, **four** in an *embryo*, **one** when develop into a **fetus** and then **two** in an **adult**.
  - **Fetal Haemoglobin (HbF)**;
    - Once an **embryo** *develops into* a **fetus** and the **four types** of **embryonic haemoglobin** ***disappear*** they are ***replaced by*** **Haemoglobin F**.
    - **Fetal Hemoglobin (HbF)**; Is the ***main*** **hemoglobin** in the **human fetus after** ***first*** **2 months** of ***development*** in the **uterus** and ***persists until*** roughly **6 months old**, normally it found to very low levels of less than 0.6% of the total hemoglobin in adults.
      - Fetal hemoglobin consist of 2-alpha and 2-gamma chains and differs from adult hemoglobin in that it is able to bind oxygen with greater affinity than the adult form, able to take its mother's oxygen which is in her bloodstream.
      - In adults, fetal hemoglobin production can be reactivated pharmacologically, which is useful in the treatment of sickle-cell disease.
  - **Adult Hemoglobin**;
    - **Hemoglobin A**; It is the major hemoglobin in adult 97% consists of 4 Polypeptide chains (2-alpha and 2-beta chains).
    - **Hemoglobin A_2**; Accounts about 2% of adult human hemoglobin and consists of 2-alpha & 2-delta chains, and is increased in Sickle-cell disease.
- **Hemoglobin Derivatives**;
  - **Hemoglobin A1c (HbA1c)** or **glycated hemoglobin**; **Hemoglobin A** ***reacts non-enzymatically*** *between* **glucose** and the **N-end** of the **beta chain** to ***form*** **Hemoglobin A1c**, ***longer*** **hyperglycemia**, the ***more*** **glucose** *binds to* **hemoglobin** and ***increase*** **glycated hemoglobin level**, **HbA1c level in plasma** ***used to*** **measure** is ***average*** of **blood glucose levels** ***during*** **three months ago** (due to the life of the RBCs; 120 days).
  - **Met-hemoglobin (Met-Hb)**; It is a **hemoglobin** in which the **iron** in the **heme group** is in the **Fe^{3+} (ferric) state**, ***not*** the **Fe^{2+}** (ferrous). **Met-hemoglobin** (*dark brown*) ***cannot*** **bind oxygen**, ***unlike*** **oxy-hemoglobin**. ***Most common*** **drugs** that can ***increase*** **level** of **Met-hemoglobin** in the **plasma** (methemoglobinemia); **Prilocaine**, **Benzocaine**, **Amyl Nitrite**, **Chloroquine**, **Dapsone**, **Nitrites**, **Nitroglycerin**, **Nitroprusside**, **Phenacetin**, **Phenazopyridine**, **Primaquine**, **Quinones** and **Sulfonamides**.
  - **Carboxy-hemoglobin (COHb** or **HbCO)**; It is **hemoglobin** ***combined with*** **carbon monoxide** (CO) ***instead*** of **oxygen** (carbon monoxide have 200 times greater affinity to Hb than oxygen). ***Conversion*** of ***most*** **Hb** to **COHb** results in **death** (**carboxyhemoglobinemia** or **carbon monoxide poisoning**). ***Smaller*** **amounts COHb** lead to **tiredness**, **dizziness** and **unconsciousness**.
  - **Sulf-hemoglobin (S-Hb)**; It is **hemoglobin** ***combined with*** **sulfur atom** (cannot be converted back to normal). S-Hb (rare occur) *produce* **anoxia** and **cyanosis** (cannot carry oxygen), under certain conditions this can be caused by drugs such as **Sulfonamides** and ***overdosing*** of **Sumatriptan**.
- **N.B.**;
  - ***Most*** **blood cells**, *including* **RBCs**, are **produced** *regularly* in **bone marrow** (a spongy material found within the cavities of many large bones).
  - ***To produce*** **hemoglobin** and **RBCs**, the **body** ***needs*** **iron**, **vitamin B_{12}**, **folate** and ***other*** **nutrients** from **foods**.

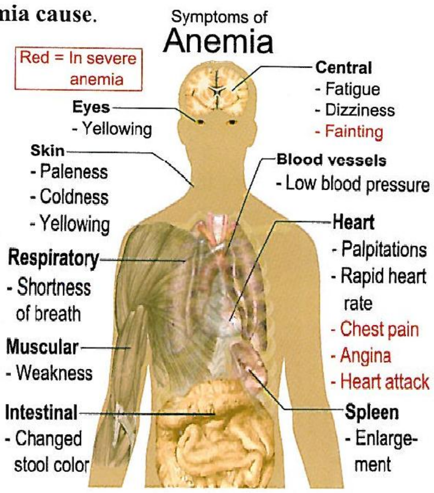
....

....

....

➢ Symptoms of Anemia :-

- **Anemia** may be **undetected** in ***many people*** and **symptoms** can be ***minor***.
- The **symptoms** can be ***related to*** **anemia cause**.
- ***Most common symptoms***;
    - Fatigue (weakness).
    - Confusion.
    - Dizziness.
    - Headache.
    - Dyspnea (shortness of breath).
    - Decrease mental activity.
    - Loss of energy.
    - Pale (yellowish) skin.
    - Fast or irregular heartbeat.
    - Chest pain.
    - Cold hands and feet.


Symptoms of
Anemia
Red = In severe anemia
Central
- Fatigue
- Dizziness
- Fainting
Eyes
- Yellowing
Skin
- Paleness
- Coldness
- Yellowing
Blood vessels
- Low blood pressure
Heart
- Palpitations
- Rapid heart rate
- Chest pain
- Angina
- Heart attack
Respiratory
- Shortness of breath
Muscular
- Weakness
Intestinal
- Changed stool color
Spleen
- Enlargement

➢ Causes and Common Types of Anemia:-

- The **causes of anemia** may be ***classified as***;

1) **Impaired RBCs production**;
    - * **Megaloblastic Anemia** (**Vitamin B_{12}** *and/or* **Folic acid** *deficiency*).
    - * **Iron Deficiency Anemia**.
    - * **Aplastic Anemia** (*rare disease in bone marrow*).
    - - **Anemia of Renal Failure** (*insufficient* **Erythropoietin** *production*).
    - - **Anemia of Endocrine Disorders** (*Hypothyroidism*).
    - - **Anemia of Chronic Inflammation** (*Cancer and inflammatory disorders*).
    - - **Anemia of Prematurity** (*due to decrease erythropoiesis at 2 to 6 weeks of age*).
2) **Increased RBCs destruction** (***hemolytic anemias***);
    - * **Enzyme Deficiencies** (Glucose-6-phosphate dehydrogenase *deficiency*).
    - * **Sickle Cell Anemia**.
3) **Blood loss**;
    - * **Hemorrhagic Anemia** (*acute or chronic blood loss*).
    - - **Anemia of Prematurity** (*due to frequent blood sampling for laboratory testing*).
    - - **Infection by Worms Feeding on Blood** (*hookworms, roundworms and whipworm*).
4) **Fluid overload** (***hypervolemia***); Fluid overload causes decreased hemoglobin concentration and apparent anemia.

➢ Risk Factors:-

- **Poor nutrition**; diet low in iron, vitamin B_{12} and folate.
- **Intestinal disorders**;, such as Crohn's disease affects the absorption of nutrients in small intestine
- **Menstruation**; due to loss of blood.
- **Pregnancy**.
- **Chronic conditions**; such as cancer, kidney failure or Hepatic failure.
- **Family history**; inherited anemia, such as sickle cell anemia.
- **Age**; people over age 65.
- **Other factors**; history of certain infections, blood diseases and autoimmune disorders, alcoholism, exposure to toxic chemicals, and the use of some medications can affect red blood cell production.

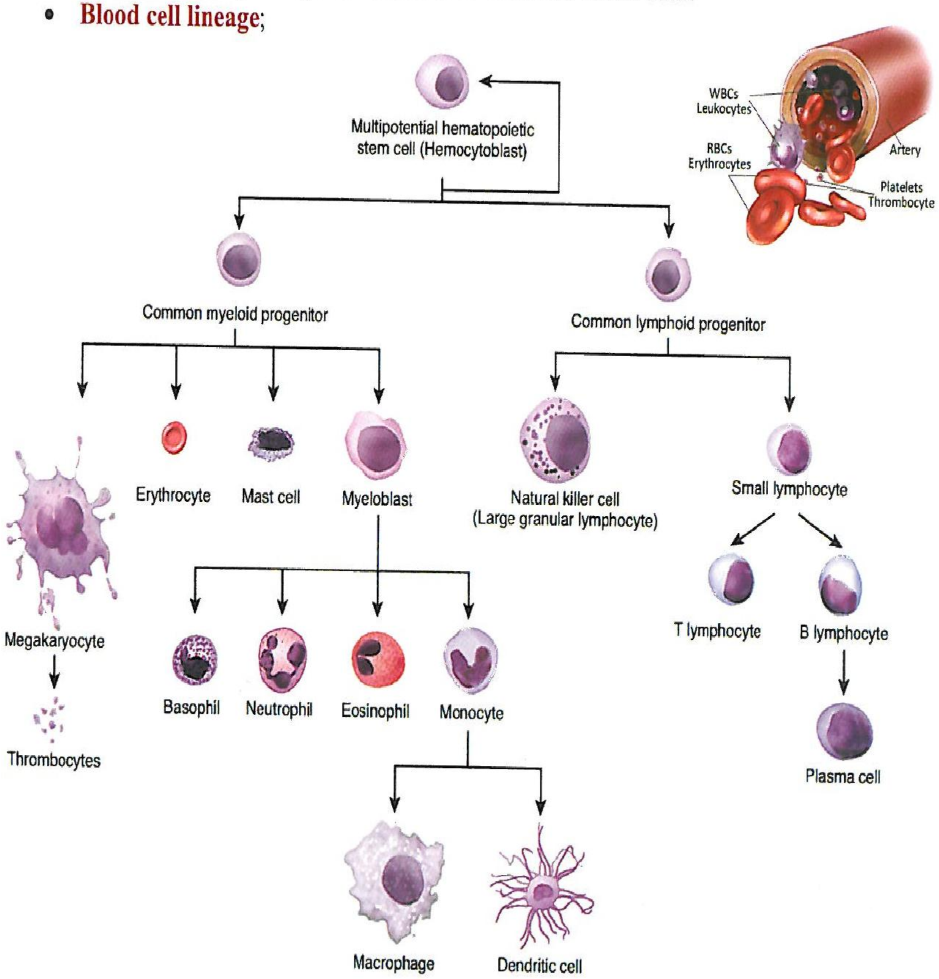
➢ Complications:-

- **Severe fatigue**.
- **Pregnancy complications** (*such as premature birth*).
- **Heart problems** (*such as arrhythmia, enlarged heart or heart failure*).
- **Death** (*such as in sickle cell anemia*).

- **Diagnosis of Anemia:** Anemia is *typically* **diagnosed** by **complete blood count (CBC)**.

Complete Blood Count (CBC)

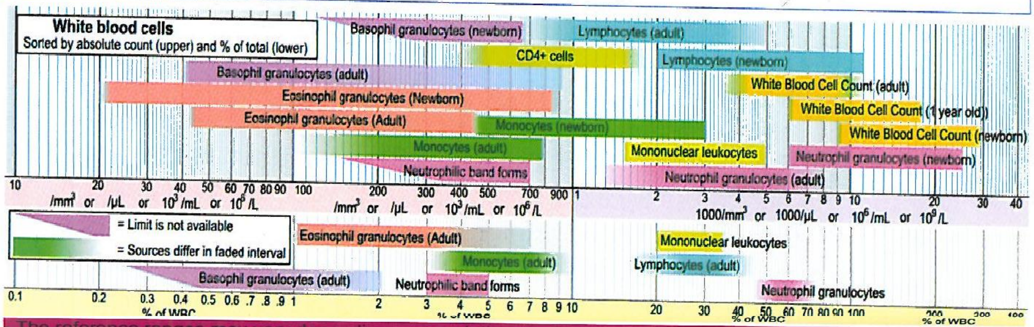
- **CBC** is a **blood panel** ***gives*** **information** about the **blood cells**.
- **Blood cell lineage**;


Multipotential hematopoietic stem cell (Hemocytoblast)
WBCs Leukocytes
RBCs Erythrocytes
Artery
Platelets Thrombocyte
Common myeloid progenitor
Common lymphoid progenitor
Megakaryocyte
Thrombocytes
Erythrocyte
Mast cell
Myeloblast
Natural killer cell (Large granular lymphocyte)
Small lymphocyte
T lymphocyte
B lymphocyte
Plasma cell
Basophil
Neutrophil
Eosinophil
Monocyte
Macrophage
Dendritic cell

- ***CBC normally include;***

I) White Blood Cells (WBCs) or Leukocytes

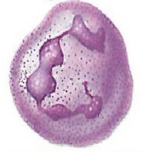
- **WBCs** are the **cells** of the **immune system** that are involved in ***protecting*** the **body *against*** both **infectious disease** and **foreign agents** and ***found in*** the **blood** and **lymphatic system**.
- ***All*** **WBCs** are ***produced*** and ***derived from*** **multipotent cells** in the **bone marrow**.
- ***All*** **WBCs** have **nuclei**, (**RBCs** and **platelets** ***not*** **have nuclei**).
- ***WBCs classification***;
  - **Granulocytes** (**Neutrophils**, **Eosinophils** and **Basophils**).
  - **Agranulocytes** (**Monocytes** and **Lymphocytes**).



- The reference ranges may vary depending on population studies, the individual laboratory, instruments & methods.

- **Total WBCs**;
  - *Reference range in adult*;
    - *Total;* 4–11 x 10^9/L or 4–11 x 10^3/mcL (4,000–11,000 WBCs per microliter).
  - ***High*** **WBC count (*leukocytosis*)**, *may result from*; (*depend on type of cell are increased*)
    - **Acute Infections**; Most commonly by bacteria and some viruses, less with fungi or parasites
    - **Acute Inflammation** or **Acute inflammatory conditions**; such as rheumatoid arthritis, vasculitis or inflammatory bowel disease.
    - **Leukemia** and **tissue necrosis** (such as trauma, burns, surgery or heart attack).
    - **Allergic responses**; (such as allergies or asthma).
  - ***Low*** **WBC count (*leukopenia*)**, *may result from* (*increased risk of infection*);
    - **Bone marrow damage**; such as toxin, chemotherapy, radiation & drugs.
    - **Bone marrow disorders**; such as myelodysplastic syndrome or cancer.
    - **Autoimmune disorders that destroys WBCs**; such as Systemic lupus erythematosus.
    - **Immune disorders**; such as HIV (human immunodeficiency virus).
    - **Other**; tuberculosis, Rickettsial infection, spleen enlargement & folate/copper/zinc deficiency.
- **WBC Differential**;

Neutrophils



- **Neutrophils** are the ***most abundant* type** of **granulocytes** (*approximately* 40-75%).
- The name **neutrophil** *derives from* **staining characteristics** (**neutrophils** *stain* a neutral pink, while **basophils** *stain* dark blue and **eosinophils** *stain* bright red).
- They ***contain*** **a nucleus *divided into* 2–5 lobes** and have a ***short*** **life span** (approximately 4 days).
- They are the ***first*** **WBCs** to **arrive** at an *area of* **inflammation** or **infection**.
- They are the ***predominant cells*** in **pus**, accounting for its whitish/yellowish appearance.
- **Mature neutrophils** are *distinguishable by* their **segmented *appearance***, thus they are often called "**Segs**" or "**Segmented**".
- **Immature neutrophils** are **non-segmented**, are known as "**Bands**" or "**Stabs**" or "**Staff**".
- *In the case of* **acute infections**, the ***body*** **reacts quickly** by ***releasing*** the **neutrophils *before*** they have ***reached*** **maturity**.
- A "**left shift**" refers to the presence of increased **immature neutrophils**.
- A "**right shift**" refers to the **immature neutrophils** are replaced with **mature neutrophils**.

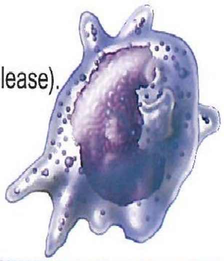
- *Reference range in adult*;
  - **Total**; 2500–7500 cells/mcL or 40–75%.
  - **Bands (Stabs or Staff)**; 150–400 cells/mcL or 3–5 %.
  - **Segmented (Segs)**; 3000–5800 cells/mcL or 37–70%.
- ***High*** **Neutrophils count (*Neutrophilia* or *Neutrocytosis*)**, *may result from*;
  - **Infections**, **injuries**, **inflammatory disorders**, **certain drugs**, **certain leukemias** and **physical** or **emotional stress**.
- ***Low*** **Neutrophils count (*Neutropenia*)**, *may result from*;
  - **Congenital**; such as Kostmann's syndrome and Myelokathexis.
  - **Bone marrow disorders**; such as Aplastic anemia and hematologic cancer (e.g. leukemia, lymphoma, myelodysplasia & myeloma).
  - **Drug immune-mediated neutropenia**; such as Quinidine, Cephalosporins, Penicillins and Sulfonamides.
  - **Autoimmune Disease**; Crohn's disease and Rheumatoid arthritis.
  - **Infections**; Bacterial sepsis, Viral infections (e.g. influenza, measles, Epstein Barr virus [EBV], cytomegalovirus [CMV], viral hepatitis, human immunodeficiency virus [HIV]), Toxoplasmosis, Brucellosis, Typhoid, Tuberculosis, Malaria and Rickettsial infection.
  - **Other drugs**; numerous drugs have been associated with neutropenia. The highest risk are; Antithyroid drugs, Macrolides, antipsychotics, antidepressants and chloramphenicol.

- ***N.B.***; **Agranulocytosis (Granulopenia)**, is **condition** involving ***marked*** **decrease** in the **number of granulocytes**, most commonly of **neutrophils *causing*** a **neutropenia**.

Lymphocytes

- **Lymphocytes** are a *part of* the **immune system**.
- The ***three* major types** of **lymphocyte** are **T cells**, **B cells** and **natural killer** (**NK**) **cells**.
- The **B cells** *produce* **antibodies** that are used to ***attack*** invading **bacteria**, **viruses** and **toxins**.
- The **T cells *destroy*** **virus-infected cells** and **tumor cells**.
- The **NK cells** play a major role in ***defending*** the **host** *from* both -**infected cells** and **tumor cells**.

- *Reference range in adult*; 1500–3500 cells/mcL or 20–40%.
- ***High*** **Lymphocytes count** (***Lymphocytosis***), *may result from*;
  - **Acute viral infections**.
  - **Toxoplasmosis**.
  - **Cancer of lymphatic system** (lymphocytic leukemia).
- ***Low*** **Lymphocytes count** (***Lymphocytopenia***), *may result from*;
  - **Certain viral infections** (such as influenza, hepatitis and AIDS).
  - **Use of corticosteroids**.
  - **Protein-energy under-nutrition** (fasting).
  - ***Severe*** **stress** or ***intense*** **physical exercise** (cortisol release).
  - **Chemotherapy** and/or **radiation therapy**.
  - **Congenital Lymphocytopenia**.



Monocytes

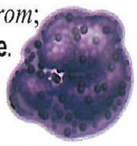
- **Monocytes** are the ***largest*** **type** of **WBCs**.
- *In the tissues*, **monocytes *mature*** *into* **macrophages** (phagocytic cells) or **dendritic cells** (antigen-presenting cells).

- *Reference range in adult*; 200–600 cells/mcL or 2–10%.
- ***High*** **Monocytes count** (***Monocytosis***), *may result from*;
  - ***Chronic*** **inflammation** or ***chronic*** **infections**.
- ***Low*** **Monocytes count** (***Monocytopenia***), *may result from*;
  - **Anything** that ***decreases*** the ***overall*** **WBCs count**.

Eosinophils

- **Eosinophils *play*** an ***important role*** in the ***defense against*** **parasitic infections**.
- ***Along with*** **mast cells**, they also ***control mechanisms*** *associated with* **allergy** and **asthma**.

- *Reference range in adult*; 30–350 cells/mcL or 1–6%.
- ***High*** **Eosinophils count** (***Eosinophilia***), *may result from*;
  - **Parasitic infections** and **allergic responses**; (such as allergies or asthma).
  - **Certain cancers** and **Addison's disease**.
- ***Low*** **Eosinophils count** (***Eosinopenia***), *may result from*;
  - **Glucocorticoid Therapy** and **Cushing Syndrome**.



Basophils

- **Basophils** are ***responsible for*** **inflammatory reactions *during*** **immune response** (such as **anaphylaxis**, **asthma**, **atopic dermatitis** and **hay fever**).
- They are ***contains*** **heparin** and **histamine**.

- *Reference range in adult*; 0-200 cells/mcL or < 1–2%.
- ***High*** **Basophils count** (***Basophilia***); **Hypothyroidism & myeloproliferative neoplasms**.
- ***Low*** **Basophils count** (***Basopenia***); **Thyrotoxicosis & hypersensitivity reactions**.

II) Platelets (Thrombocytes)

- **Platelets** (**Thrombocytes**) are ***fragments*** of **megakaryocytes** which are ***formed*** in the **bone marrow**.
- They are ***essential*** to **hemostasis** and **blood clotting**.
- They are ***circulate*** in the **bloodstream** for a **life span** of **8-10 days**.

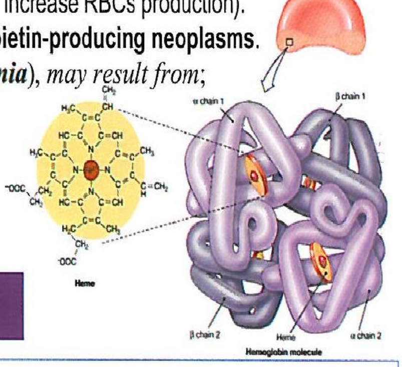
- *Reference range in adult*; 150–400 x 10^3/mcL
- ***High*** **Platelets count** (***thrombocytosis*** and ***thrombocythemia***), *may result from*;
  - **Essential thrombocythemia** (elevated & activated); **myeloproliferative disorder**.
  - **Reactive thrombocytosis** (**secondary thrombocythemia**; not typically associated with an increased risk of thrombosis); **acute infection**, **chronic inflammatory disorders**, **iron deficiency** and **certain cancers**.
- ***Low*** **Platelets count** (***thrombocytopenia***), *may result from*;
  - **Immune thrombocytopenia** (**ITP**).
  - **Thrombocytopenia accompanying systemic infection.**
  - **Gestational thrombocytopenia.**
  - **Drug-induced thrombocytopenia** (commonly, heparin and certain chemotherapy).
  - **Splenomegaly.**
- ***Some peoples*** have ***normal*** **platelet count** *but* have **platelet dysfunction** may stem from an intrinsic platelet defect or from an extrinsic factor that alters the function of normal platelets. Dysfunction may be hereditary or acquired (antiplatelet drugs).

III) Red Blood Cells (RBCs) or Erythrocytes

- **RBCs** are *responsible for* ***delivering*** **oxygen** to the **body tissues**.
- They are ***rich in*** **hemoglobin** that can ***bind*** to **oxygen**.
- They are ***develops in*** the **bone marrow** and ***circulate for*** about **100-120 days**.

- *Reference range in adult*;
  - **Male**; 4.5–5.9 million cells/mcL.
  - **Female**; 4.1–5.1 million cells/mcL.
- ***High*** **RBCs count** (***erythrocytosis*** or ***polycythemia***), *may result from*;
  - **Stress** and **smokers**.
  - **High altitude.**
  - **Hemoconcentration** and **dehydration.**
  - **Cardiovascular disease** (**congenital heart disease**).
  - **Polycythemia vera** (bone marrow disease; increase RBCs production).
  - **Renal cell carcinoma** and other **erythropoietin-producing neoplasms.**
- ***Low*** **RBCs count** (***anemia*** or ***erythroblastopenia***), *may result from*;
  - **Anemias.**
  - **Hemolysis.**
  - **Chronic renal failure.**
  - **Hemorrhage.**
  - **Failure of marrow production.**

Hemoglobin

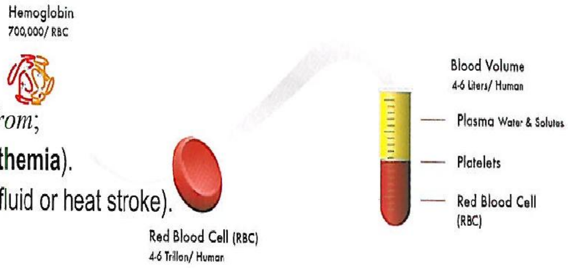


- **Hemoglobin** (**Hb** or **Hgb**); is the ***iron-containing oxygen-transport metalloprotein*** in the **red blood cells.**
- **Hemoglobin** has **two parts**; **heme** (prosthetic group) and **goblin** (Protein).

- *Reference range in adult*;
  - **Male**; 13–17 grams/dL = 130-170 grams/L.
  - **Female**; 12–15 grams/dL = 120-150 grams/L.
- ***High*** **hemoglobin count**; **causes** that ***increase*** **RBCs** ***count***.
- ***Low*** **hemoglobin count**; **anemias** and *other* **causes** that ***decrease*** **RBCs** ***count***.

Hematocrit (Hct)

- **Hematocrit** (**Hct**) or **Packed Cell Volume** (**PCV**); is the **volume *percentage*** (vol %) of **RBCs *in* blood**.
- It was determined by centrifuging heparinized blood in a capillary tube, but now the hematocrit is calculated by an **automated analyzer**.


Hemoglobin
700,000/ RBC
Red Blood Cell (RBC)
4-6 Trillon/ Human
Blood Volume
4-6 Liters/ Human
Plasma Water & Solutes
Platelets
Red Blood Cell
(RBC)

- *Reference range in adult*;
  - **Male**; 40-50%.
  - **Female**; 35-45%.
- ***High* Hct value**, *may result from*;
  - **Erythrocytosis** (**polycythemia**).
  - **Dehydration** (decrease fluid or heat stroke).
  - **Fall in plasma levels**.
  - **Congenital heart disease**.
  - **Pulmonary conditions** (**sleep apnea** or **COPD**).
  - **Hypoxia** (high altitude, premature babies with delayed lung development).
- ***Low* Hct value**, *may result from*;
  - **Anemias** and **overhydration**.
  - **Bone marrow *suppression*** or ***underproduction*** (**leukemia** and **chemotherapy**).
  - **Bleeding**, **red blood cell destruction** and **pregnancy**.

Mean Corpuscular Volume (MCV)

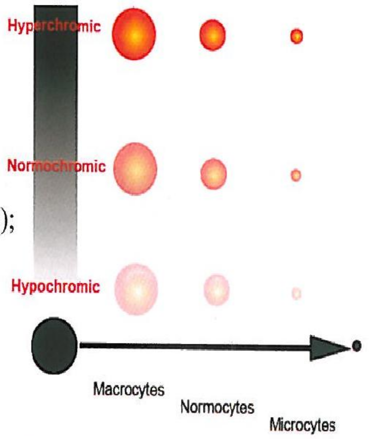
- **Mean Corpuscular Volume** or **Mean Cell Volume** (**MCV**); is the ***average* volume** of **RBC**.
- ***Calculated by***; ***dividing*** the **Hematocrit** (**Hct**) ***by*** the **concentration of RBCs**.

- *Reference range in adult*; 80–100 fL (Femtoliter = 10^{-15} liter).

Mean Corpuscular Hemoglobin (MCH)

- **Mean Corpuscular Hemoglobin** or **Mean Cell Hemoglobin** (**MCH**); is the ***average* content** (***mass***) of **Hb *per* RBC** in a **blood sample**.
- ***Calculated by***; ***dividing*** the **total mass of hemoglobin *by*** the **number of RBCs**.
- ***Bigger* RBCs** *usually have* ***more*** **hemoglobin** and ***smaller* RBCs** *usually have* ***less*** **hemoglobin**.

- *Reference range in adult*; 27–33 picograms/cell (picograms = 10^{-12} gram).
- ***High* MCV** and **MCH values** (***macrocytic anemia***) *may result from*;
  - **Folate deficiency anemia**.
  - **Vitamin B_{12} deficiency anemia**.
  - **Liver disease** (**cirrhosis** & **alcohol abuse**).
  - **Hypothyroidism** (**Myxedema**).
  - **Myelodysplastic syndrome**.
- ***Low* MCV** and **MCH values** (***microcytic anemia***);
  - **Iron deficiency anemia**.
  - **Thalassemia**.
  - **Anemia of chronic disease**.
  - **Sideroblastic anemia**.
  - **Lead poisoning**.


Hyperchromic
Normochromic
Hypochromic
Macrocytes
Normocytes
Microcytes

- ***Low* hemoglobin count** with ***normal*** **MCV** and **MCH values** (***normocytic anemia***);
  - **Acute blood loss**.
  - **Hemolytic anemia**.
  - **Aplastic anemia**.

Mean Corpuscular Hemoglobin Concentration (MCHC)

- **Mean Corpuscular Hemoglobin Concentration** (**MCHC**); is the ***average*** **hemoglobin concentration** ***relative to*** the **size** of the **RBC**. ***Calculated by***; ***dividing*** the **hemoglobin** by the **hematocrit**.

- *Reference range in adult*; 33–36 g/dL.
- ***High*** **MCHC value** (***hyperchromic anemia***) *may result from*;
  - **Folate deficiency anemia.**
  - **Vitamin B_{12} deficiency anemia.**
  - **Hereditary spherocytosis.**
- ***Low*** **MCHC value** (***hypochromic anemia***) *may result from*;
  - **Iron deficiency anemia.**
  - **Thalassemia**, **lead poisoning**, **anemia of chronic disease** and **sideroblastic anemia**.

Red Cell Distribution Width (RDW)

- **Red Blood Cell Distribution Width** (**RDW** or **RDW-CV** or **RCDW** and **RDW-SD**) is a ***measure of*** the **range** of **variation** of **RBC volume** or **RBC size**.
- This is **important** to ***differentiate between*** **iron deficiency anemia** (***increased***) and **thalassemia** (***normal***).

- *Reference range in adult*; 11.5–14.5%.
- ***High*** **RDW value** *may result from*;
  - **Iron deficiency anemia** (*with* low MCV).
  - **Folate deficiency anemia** and **Vitamin B_{12} deficiency anemia** (*with* high MCV).
  - **Liver disease** {**cirrhosis** & **alcohol abuse**} (*with* high MCV).

➢ Summary:-

- **Normocytic/Normochromic** (**NC/NC**) **anemia**, *may result from*; Hemolytic anemia, sudden blood loss (hemorrhagic anemia), aplastic anemia, prosthetic heart valves, blood infection (sepsis), tumor, long-term disease or renal disease anemia.
- **Microcytic/Hypochromic anemia**, *may result from*; Iron deficiency anemia, thalassemia or lead poisoning.
- **Macrocytic/normochromic** or **hyperchromic anemia**, *may result from*; folate deficiency, vitamin B_{12} deficiency anemia or chemotherapy.
- **N.B**; Vitamin B_{12} deficiency anemia may be normochromic or hypochromic if associated with Iron deficiency anemia.
- **Hyperchromic anemia** is an anemia with increase of hemoglobin in individual red blood cells and reduction in the number of red blood cells.
- **C-reactive protein** (**CRP**); is a protein found in blood plasma, whose levels rise (< 3 mg/L) in response to **inflammation** (Acute or chronic inflammatory conditions or Infection, tissue necrosis, injury or burns, Ischemia or infarction of issues, malignant tumors, Leukemia, smoking and obesity).
- **Iron tests** (**serum iron**, **total iron binding capacity** & **ferritin level**); may be important to confirm diagnosis

➢ Erythrocyte Sedimentation Rate (ESR):-

Erythrocyte Sedimentation Rate (ESR)

- **Erythrocyte Sedimentation Rate** (**ESR**) or **sedimentation rate**; is the ***rate*** at which **RBCs** ***sediment*** in a **period** of **one hour**. It is a common hematology test (*not CBC*) & is a ***non-specific*** measure of inflammation.

- *Reference range in adult*; 11.5–14.5%.
  - **Men** < 50 years old: < 15 mm/hr.
  - **Men** > 50 years old: < 20 mm/hr.
  - **Women** < 50 years old: < 20 mm/hr.
  - **Women** > 50 years old: < 30 mm/hr.
- ***High*** **ESR value** *may result from*; inflammation, pregnancy, anemia, autoimmune disorders, infections, some kidney diseases and some cancers.
- ***Low*** **ESR value** *may result from*; polycythemia, hyperviscosity, sickle cell anemia, low plasma protein and congestive heart failure.

➢ Common Types of Anemia:-

A) Normocytic-Normochromic Anemia

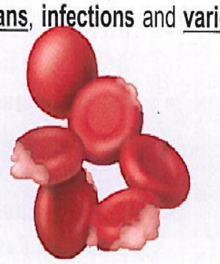
- **Normocytic-Normochromic anemia**: is a ***blood disorder*** characterized by **normal amounts** of **haemoglobin** ***within*** **normal-sized RBCs**. The ***number*** of **RBCs** is **low**.
- **Normocytic-Normochromic anemia** ***such as*** **haemolytic anemia**, **aplastic anemia**, **hemorrhagic anemia**, and **chronic diseases**.

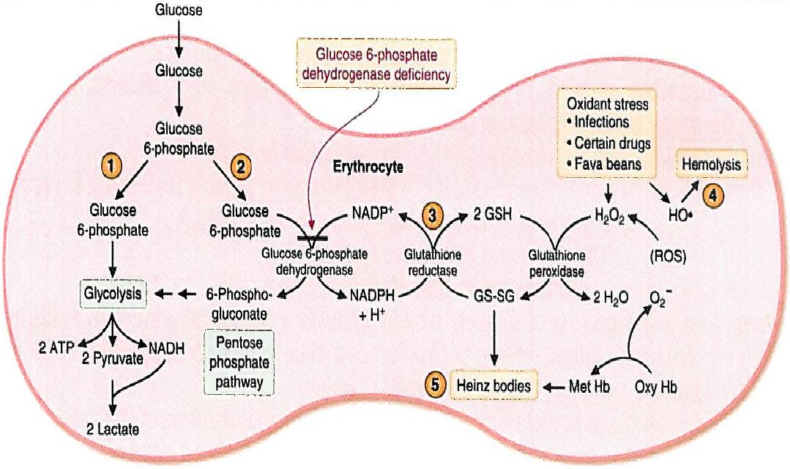
I) Hemolytic Anemia

- **Hemolytic anemia**; is a ***form of*** **anemia** ***due to*** **hemolysis** (*abnormal breakdown of RBCs*).
- ***Common* causes**;
  - **Intrinsic causes** (***Genetics***);
    - **Defects of RBC membrane production** (such as in **hereditary spherocytosis**).
    - **Defects in hemoglobin production** (such as in **thalassemia** and **sickle-cell disease**).
    - **Defective red cell metabolism** (such as in **glucose-6-phosphate dehydrogenase *deficiency*** and **pyruvate kinase *deficiency***).
  - ***Extrinsic causes*** (***Acquired***);
    - **Immune-mediated causes**; **infection**, **autoimmune diseases** or **certain drugs**.
    - **Incompatible blood transfusion**.
    - **Patients who are recipients prosthetic heart valve**.
    - **Hypersplenism** (*increased activity of the spleen*); such as **portal hypertension**.
    - **Runners** (*mechanical hemolytic anemia*).
    - **Lead poisoning**.

Glucose-6-phosphate Dehydrogenase Deficiency Anemia (Favism)

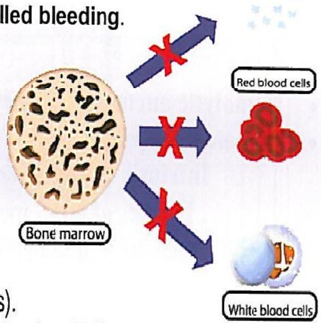
- **Glucose-6-phosphate dehydrogenase** (**G-6-PD**) is an ***essential enzyme*** for ***normal*** **life span** for **RBCs**, and ***prevent*** **RBCs damage** *from* **oxidizing processes**.
- This ***enzyme deficiency*** may ***provoke*** the ***sudden*** **destruction** of **RBCs** and *lead to* **hemolytic anemia** with **jaundice** in ***response*** to a **number of triggers**, ***such as***; *intake* of **fava beans**, **infections** and **various drugs**, the following are considered ***high risk***:
  - **Primaquine**, **Pamaquine** and **Chloroquine** (*antimalarial agents*)
  - **Sulfonamides** (*Antibiotics*).
  - **Non-sulfa antibiotics** (**Nalidixic acid**, **Ciprofloxacin**, **Nitrofurantoin**, **Chloramphenicol**, **Isoniazid**, **Dapsone** and **Furazolidone**).
  - **Glibenclamide** (*antidiabetic drug*).
  - **Rasburicase** (*recombinant urate oxidase*).
- **G-6-PD enzyme** *responsible for* ***convert*** **NADP+** to **NADPH** which *make* ***detoxification*** of the **drugs** or **toxic agents** *through* **glutathione system**.
- The deficit is most prevalent in **Africa** (affecting up to 20% of the population).




Glucose
Glucose
Glucose 6-phosphate
Glucose 6-phosphate dehydrogenase deficiency
Erythrocyte
Oxidant stress
• Infections
• Certain drugs
• Fava beans
Hemolysis
1
2
3
4
5
Glucose 6-phosphate
Glucose 6-phosphate
NADP+
2 GSH
H2O2
HO•
Glucose 6-phosphate dehydrogenase
Glutathione reductase
Glutathione peroxidase
(ROS)
Glycolysis
6-Phospho-gluconate
NADPH + H+
GS-SG
2 H2O
O2−
2 ATP
2 Pyruvate
NADH
Pentose phosphate pathway
Heinz bodies
Met Hb
Oxy Hb
2 Lactate

II) Aplastic Anemia

- ***Aplastic anemia***; is a ***rare disease*** in which the **bone marrow *stops* producing enough new blood cells.**
- This causes a ***deficiency*** of **all three blood cell types (pancytopenia): red blood cells (*anemia*), white blood cells (*leukopenia*) and platelets (*thrombocytopenia*).**
- ***Complications***; **fatigue, high risk of infections** and **uncontrolled bleeding.**
- ***Prevalence***; *approximately* **two *per* million.**
- ***Causes***;
  - **Idiopathic** (*Unknown*).
  - **Genetics.**
  - **Certain viral infections.**
  - **Immune disease.**
  - **Pregnancy.**
  - *Exposure to* **radiation.**
  - *Exposure to* **certain chemicals** (Benzene or Pesticides).
  - *Exposure to* **certain drugs** (Chloramphenicol, Carbamazepine, Felbamate, Phenytoin and Quinine).
- ***Treatments***; **Blood transfusion, stem cell transplant, immunosuppressants** or **bone marrow stimulants.**

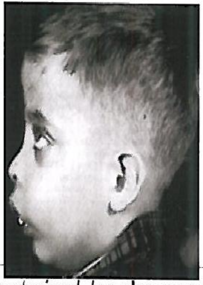


III) Hemorrhagic Anemia

- **Anemia** *due to* **excessive bleeding.**
- ***Rapid*** (or **acute**) ***blood loss***; **symptoms of anemia** *develops **rapidly*** from a ***sudden*** **blood loss**, such as from an **injury, surgery**, or **childbirth.** ***Treatments***; **blood transfusion.**
- ***Chronic blood loss***; such as that from **nosebleeds, hemorrhoids** and **GI ulcers** and **menstrual bleeding.** ***Treatments***; *usually* **iron supplements *until* anemia are resolved.**

B) Microcytic Anemia

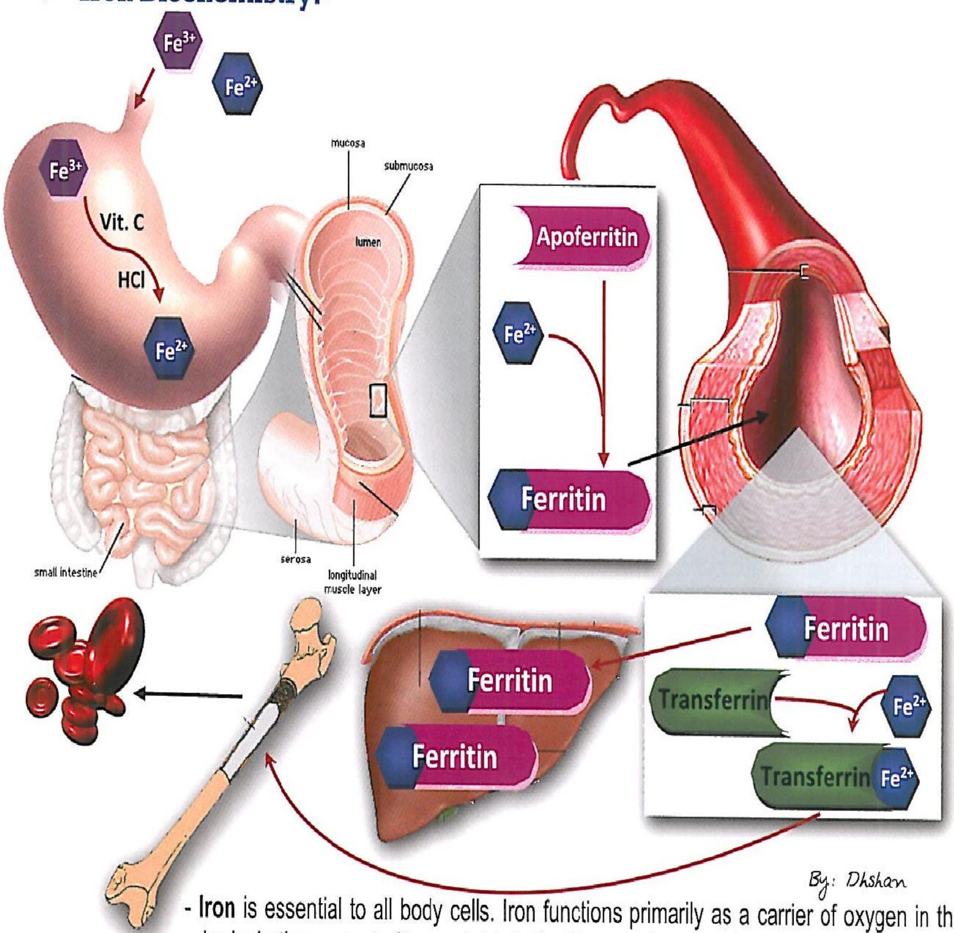
- **Microcytic anemia**; is ***any type*** of **anemia** *characterized by **small*** **RBCs** (*low* **MCV & MCH**). The **microcytic anemia** are ***usually*** **hypochromic** (*low* **MCHC**).
- The ***main*** **causes of microcytic anemia**;
  - **Iron deficiency anemia.**
  - **Anemia of chronic disease.**
  - **Thalassemia.**
  - **Sideroblastic anemia.**
- The ***main*** **causes of microcytic hypochromic anemia**;
  - **Thalassemia** and **iron deficiency anemia.**



I) Thalassemia

- **Thalassemia** [thal-uh-SEE-me-uh] is a *group* of **inherited blood disorder** *characterized by* **abnormal formation of hemoglobin.** The **name** is ***derived from*** the **Greek word "thalassa"** meaning **"the sea"** because it was ***first described*** in populations living near the **Mediterranean Sea.**
- **Thalassemia** is ***caused by*** **mutation** in **genes** that ***makes*** **hemoglobin**, cause ***defects in*** either the **α** or **β globin chain.** ***Common types*** of **thalassemia**;
  - **α-thalassemia.**
  - **β- thalassemia**; 1) **β-thalassemia major** or **Mediterranean anemia** (*no* **HbA** and *most* **severe**).
    - 2) **β-thalassemia intermedia** (*some* **hemoglobin A**).
    - 3) **β-thalassemia minor** (*less severe*).
      - **β-thalassemia *prevalence***; *approximately* **1** in **100,000.**
- ***Complications***; **Iron overload** (*due to frequent blood transfusions*), **heart failure** and **liver fibrosis** (*due to iron overload*) and **enlarged spleen** (*due to destruction of a large number of RBCs*) and **bone deformities** (especially in the face and skull; *see photo* **thalassemia face**).
- About 5% of the population are carriers one or other of the most serious forms of thalassemias, which are believed to provide protection against malaria, and it is thought that has been responsible for elevating and maintaining their gene frequencies.

➢ Iron Biochemistry:-



By: Dhshan

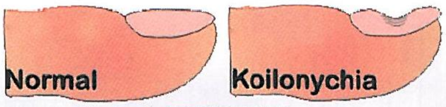
- **Iron** is essential to all body cells. Iron functions primarily as a carrier of oxygen in the body, both as a part of hemoglobin in the blood and myoglobin in the muscles.
- Iron deficiency anemia occurs when there is not enough iron in the red blood cells.

- **Dietary Iron**;
  - **In animal foods**; **iron** is often *attached to* proteins called **heme** proteins, and referred to as **heme iron** (*more easily absorbed*).
  - **In plant foods**; **iron** is ***not attached*** to **heme** proteins and is classified as **non-heme iron**.
  - The amount of **dietary iron *absorbed*** is typically **low** (5-35%).
  - *About* **4-5 grams** of **iron** in the **body**, *about* **2.5 g** is ***contained*** in the **hemoglobin**.
- **Iron Ions**;
  - **Iron** (**Fe**) can exist in ***more than*** **one chemical form**, (or oxidation state), the **two *most common forms*** for iron are; - **Ferrous state** (Fe^{2+}); iron ion shares two of its electrons.
    - **Ferric state** (Fe^{3+}); iron ion shares three of its electrons.
- **Iron Absorption**;
  - ***To be absorbed***; **iron *must be*** in its ferrous (**Fe^{2+}**) **form**.
  - The first step in iron absorption requires the ***reduction*** of **ferric iron** (Fe^{3+}) to **ferrous iron** (Fe^{2+}) by **duodenal ferric reductase** ***enzyme***.
  - **Iron absorption *from diet*** is ***enhanced*** in the presence of **vitamin C** and ***decreased by excess*** **calcium, zinc, manganese** or ***large amounts*** of **tea** or **coffee**.
  - The **intestinal mucosa *contains*** a **protein** called "**Apoferritin**" which ***combines*** with **Fe^{2+}** to form **ferritin**.
  - **Iron absorption *stop*** when ***all*** **Apoferritin *converted to*** **Ferritin**.
  - The blood contain **protein** called "**transferrin**", ***carries*** **iron** *to* **bone marrow** to *form* **RBCs**.
  - **Iron** are ***stored in*** **deferent tissues** as **liver, spleen & bone marrow** in the form of **ferritin**.

- *N.B.*; **Iron** is an ***essential*** **bioelement** for ***most forms of life***, from **bacteria** to **mammals;** in ***acute infections***, it is generally thought that **IV iron *should be*** **avoided** in ***patients*** who have ***active*** **bacterial infections**.
  - ***Iron tests*** (**serum iron**, **total iron binding capacity** & **ferritin level**); may be important to confirm diagnosis.

II) Iron Deficiency Anemia (IDA)

- **Iron Deficiency Anemia**; is **anemia** *caused by* a **lack of iron**.
- *Prevalence*; *approximately* **half** of **all anemia cases worldwide**, affects **women** *more often than* **men**. **Iron deficiency anemia** *affected* **1.2 billion** people in 2013.
- *CBC results*; *Low* **MCV** and **MCHC**.
- *Signs*;
  - ** Koilonychia (spoon-shaped nails).
  - ** Pallor (reduced oxyhemoglobin in skin or mucous membranes).
  - Pica (hunger for ice, dirt and paper).
  - **Cracked corners** of the **mouth**.



Cracked corners of the mouth

- *Causes*;
  - **Blood loss**; *heavy* **menstrual periods**, **GI bleeding**, **parasitic disease** and **hemorrhoids**.
  - **Lack of iron in diet**; *examples of* **iron-rich foods**; **Chicken liver**, **meat**, **leafy green vegetables**, **beans**, **seafood** (*especially* oysters), **fortified breakfast cereals** and **nuts**.
  - **Lack of iron absorption**.
  - **Pregnancy**; occurs in *many* **pregnant women**.
- *Recommended Dietary Allowance (RDA)*;
  - **Pre-menopausal women**; 18 mg/day.
  - **Men** and **post-menopausal women**; 8 mg/day.
  - **Pregnancy**; 27 mg/day. - **Lactation**; 10 mg/day.

Chicken liver

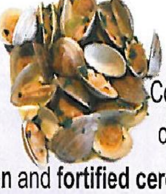
- **Treatments**; *eating more* **iron-rich foods** or *taking* **iron supplements** (**IV iron** or **blood transfusions** *can be administered*); see hematopoietic drugs.

C) Macrocytic Anemia

- **Macrocytic anemia**; is a *class of anemia* in which **RBCs** are *larger than* **normal volume**.
- **Macrocytic anemia** are *associated with* ***insufficient*** **numbers** of **cells** and often also ***insufficient*** **hemoglobin content** (i.e. total blood hemoglobin concentration that is less than normal). The ***most*** **common type** of **macrocytic anemias** is **megaloblastic anemia**.

I) Megaloblastic Anemia

- **Megaloblastic anemia**; is an anemia that ***results from*** **inhibition of DNA synthesis** during **RBCs production**;
  - *When* **DNA synthesis** is ***impaired***, the **cell cycle** ***cannot*** **progress** from the **growth stage** ***to the*** **mitosis stage**, this *leads to* ***continuing*** **cell growth** ***without*** **division**. The ***defect*** in **RBC DNA synthesis** is most often *due to* ***deficiency of*** **Vitamin B_{12}** and/or **Folic acid**.
- *CBC results*; *High* **MCV** and **MCHC**.
- *Causes*;
  - *For* **Vitamin B_{12} (Cobalamin)**;
    - **Lack of vitamin B_{12} in diet**; *examples of* **cobalamin-rich foods**;
      - **Cooked clams (shellfish)**, **meat**, **liver**, **fish**, **chicken** and **fortified cereals**.
    - **Failure in intrinsic factor "IF"** (pernicious anemia); *see vitamin B_{12} biochemistry.*
    - **Coeliac** [see-L-i-ak] **disease** (autoimmune disease in small intestine; malabsorption of vitamins).
    - **Chronic pancreatitis** and ***prolonged*** *exposure* to **nitrous oxide**.

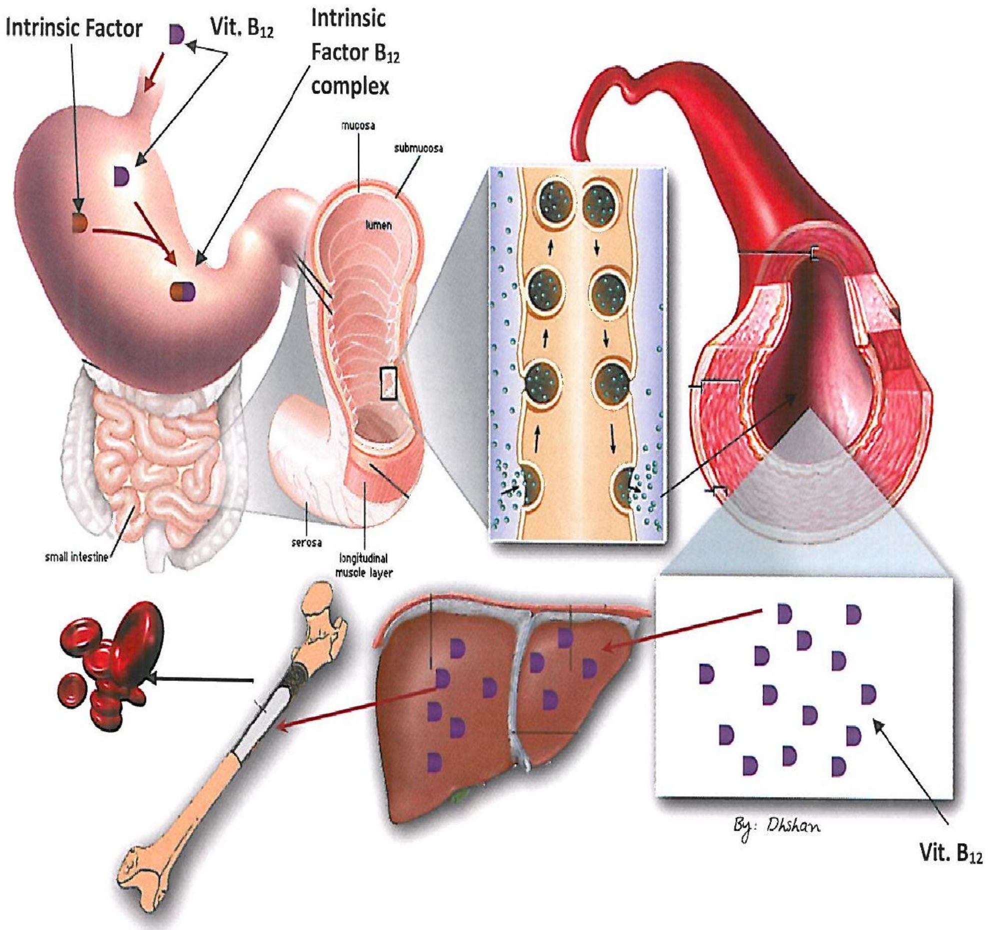

Cooked clams

  - *For* **Folate (Vitamin B_9)**;
    - **Lack of folate in diet**; *examples of* **folate-rich foods**;
      - **Spinach**, **cowpeas**, **lentils**, **broccoli**, **bread** & **fortified cereals**.
    - **Increased demand**: **pregnancy**, **infant**, **rapid cellular proliferation** and **renal dialysis**.
    - **Alcoholism**; *impaired folate bioavailability.*
    - **Intestinal disorders**; *impaired* folate absorption (malabsorption).
    - **Medications**; **methotrexate**, **sulfonamides**, **trimethoprim**, **phenytoin**, **metformin** & **valproic acid**.

Cooked spinach

- *Recommended Dietary Allowance (RDA)*;
  - *For* **Vitamin B_{12}**; *Adult*; 2.4 mcg/day - ***Pregnancy***; 2.6 mcg/day - ***Lactating women***; 2.8 mcg/day.
  - *For* **Folate**; *Adult*; 400 mcg/day - ***Pregnancy***; 600 mcg/day - ***Lactating women***; 500 mcg/day.
- **Treatments**; *eating more* **cobalamin/folate-rich foods** or *taking* **Vitamin B_{12}/Folate supplements**; see hematopoietic drugs.

➢ Vitamin B_{12} Biochemistry:-



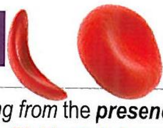
- **Vitamin B_{12} Absorption**;
  - **Vitamin B_{12}** is ***called*** **extrinsic factor** and its ***need*** **a protein** called **intrinsic factor** for **absorption**.
  - The **intrinsic factor** is ***secreted by*** **gastric parietal cells**.
  - The **intrinsic factor** ***combine with*** **vitamin B_{12}** to form **intrinsic factor B_{12} complex** which ***absorbed by*** pinocytosis in ***lower part*** **small intestine** (**ileum**).
  - **Vitamin B_{12}** is ***stored*** in **large amount** in **liver**.
  - It ***released slowly*** from **liver** as *needed by* **bone marrow** for *formation of* **new RBCs**.

- *N.B.*;
  - **Vitamin B_{12}** ***deficiency*** can *cause* **severe** and ***irreversible*** **nerve damage**.
  - **Vitamin B_{12}** *plays* an *important role* in the ***maintenance*** of the **myelin sheaths** that *cover* and *protect* the nerves, ensuring proper and faster nerve-impulse transmission.
  - ***Large amounts*** of **Folic acid** (>1,000 µg/daily) can ***mask*** the **damaging effects** of **vitamin B_{12}** ***deficiency*** by ***correcting*** the **megaloblastic anemia** *caused by* **vitamin B_{12}** ***deficiency*** ***without*** **correcting** the **neurological damage** that *also occurs*. ***To counter*** the ***masking effect*** of **vitamin B_{12}** ***deficiency*** the **National Institutes of Health** (NIH) ***recommends*** **Folic acid** intake from **fortified food** and **supplements** ***should not exceed*** **1,000 µg daily** in healthy adults.

II) Pernicious Anemia

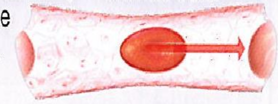
- **Pernicious anemia**; is an anemia that *results from* ***lack of*** **intrinsic factor (IF)**, *lead to* ***lack of*** **absorption** of **vitamin B_{12}** (**vitamin B_{12}** is ***absorbed*** in the **small intestine** (ileum) after ***binding to*** **intrinsic factor**). **Intrinsic factor** is ***produced by*** **gastric parietal cells**.
- ***CBC results***; ***High*** **MCV** and **MCHC**.
- ***Causes***; **Failure in intrinsic factor**; functional failure or failure in cell producing IF (autoimmune destruction).
- **Treatments**; **Vitamin B_{12} (cobalamin) supplements**; see hematopoietic drugs.

III) Sickle Cell Anaemia (SCA)



- **Sickle Cell Disease** (**SCD**); is a ***group of*** **genetic blood disorders**, *resulting from* the ***presence of*** a ***mutated*** form of **hemoglobin** (**hemoglobin-S**), the ***most common type*** is known as **Sickle Cell Anaemia** (**SCA**).
- In **sickle cell anemia**, the **hemoglobin** *become* **abnormal** and ***can't*** **carry oxygen**, It results ***low*** **oxygen tension** ***promotes*** RBC ***sickling*** and ***decrease*** the **cell's elasticity**.
- These ***rigid*** **blood cells** are ***unable*** to **pass** *through* narrow **capillaries**, ***leading to*** **vessel occlusion**.
- ***Healthy*** **RBCs** ***typically*** function for **90–120 days**, but **sickled cells** ***only*** last **10–20 days**.
- *Complications*; **SCD** may lead to various ***acute*** and ***chronic*** **complications**, with ***high*** **mortality rate**;
  - **Vaso-occlusive crisis**; obstruction in capillaries and restrict blood flow to an organ resulting in ischemia, pain, necrosis and often organ damage (*particularly* **spleen**).
  - **Acute chest syndrome** (**ACS**); is a vaso-occlusive crisis of the pulmonary vasculature; chest pain, fever, pulmonary infiltrate.
  - **Anemia**; *due to* ***fast*** **RBCs** ***break down***.
  - **Aplastic crisis**; due to decrease reticulocyte counts during the disease, lead to rapid drop in hemoglobin (this crisis takes 4 days to one week to disappear).
  - **Hemolytic crisis**; ***acute accelerated*** in **RBCs** ***break down***.

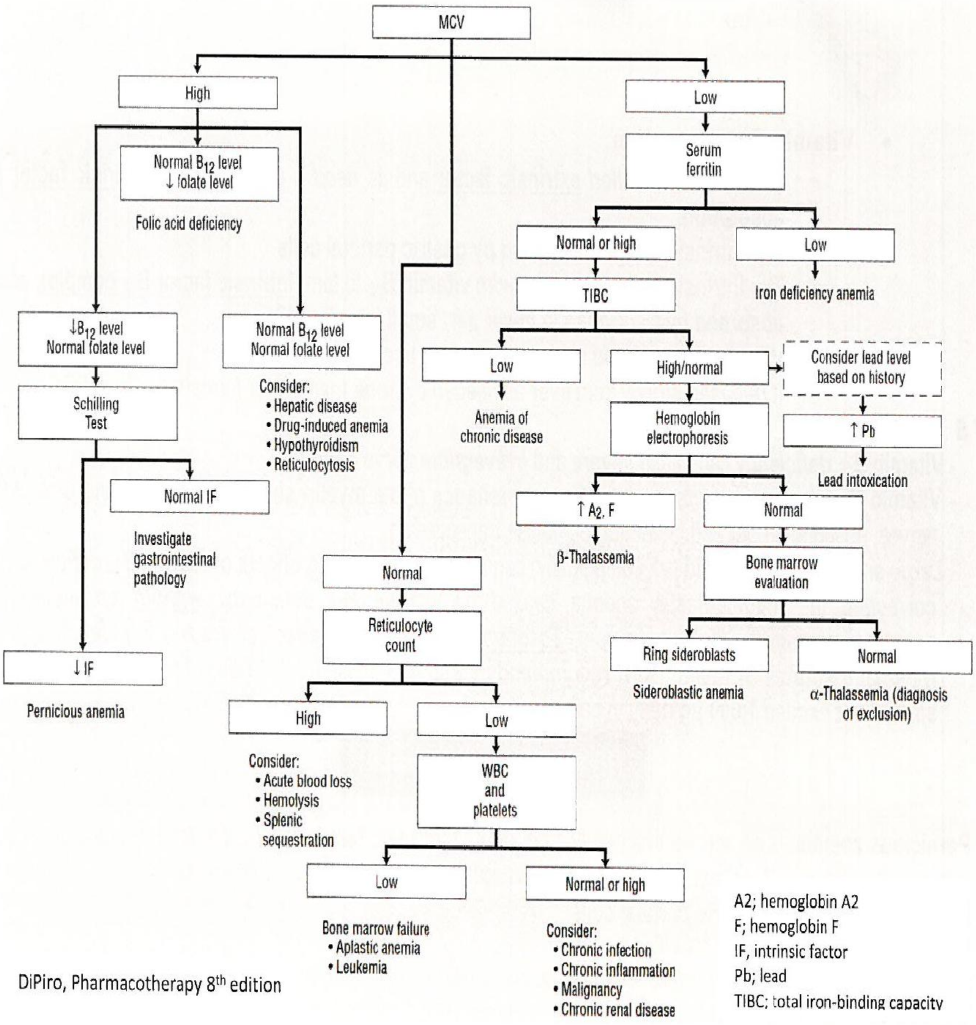
Normal Cells



Sickle Cell Disease

- *N.B.*; **Sickle-cell crisis**; is ***severe acute conditions*** including the **vaso-occlusive crisis**, **aplastic crisis** and **hemolytic crisis**.
- **Treatments**; *There's* ***no cure***, **treatments** can ***relieve*** **pain** and help ***prevent*** **further problems** ***associated with*** **sickle cell anemia**; see hematopoietic drugs.

➢ General Algorithm for Diagnosis of Anemias:-


MCV
High
Normal B12 level
↓ folate level
Folic acid deficiency
↓B12 level
Normal folate level
Schilling Test
Normal IF
Investigate gastrointestinal pathology
↓ IF
Pernicious anemia
Normal B12 level
Normal folate level
Consider:
• Hepatic disease
• Drug-induced anemia
• Hypothyroidism
• Reticulocytosis
Normal
Reticulocyte count
High
Consider:
• Acute blood loss
• Hemolysis
• Splenic sequestration
Low
WBC and platelets
Low
Bone marrow failure
• Aplastic anemia
• Leukemia
Normal or high
Consider:
• Chronic infection
• Chronic inflammation
• Malignancy
• Chronic renal disease
Low
Serum ferritin
Normal or high
Low
Iron deficiency anemia
TIBC
Low
Anemia of chronic disease
High/normal
Consider lead level based on history
↑ Pb
Lead intoxication
Hemoglobin electrophoresis
↑ A2, F
β-Thalassemia
Normal
Bone marrow evaluation
Ring sideroblasts
Sideroblastic anemia
Normal
α-Thalassemia (diagnosis of exclusion)

A2; hemoglobin A2
F; hemoglobin F
IF, intrinsic factor
Pb; lead
TIBC; total iron-binding capacity

DiPiro, Pharmacotherapy 8th edition

Hematopoietic Drugs

A) Drugs for Anemia

- Erythropoietin
- Iron Supplements
- Folic Acid
- Vitamin B12
- Drugs for Sickle Cell Disease

Erythropoiesis-Stimulating Agents (ESAs)

Epoetin alfa (Epiao®) (Eprex®) | **Epoetin beta** (NeoRecormon®)

Darbepoetin alfa (Aranesp®)

Methoxy polyethylene glycol-epoetin beta (Mircera®)

- **Erythropoietin** [eerith-ro-POI-eh-tin] (**EPO**); is a ***glycoprotein hormone*** that ***controls*** **erythropoiesis** (*RBCs production*).
- **Peri-tubular cells** in the **kidneys** ***work as*** **sensors** that ***respond*** to **hypoxia** and ***mediate*** **synthesis** and **release** of **EPO**.
- ***Recombinant*** **human erythropoietin**; **rhEPO** (**Epoetin alfa**, **Epoetin beta** and **Darbepoetin alfa**), *produced by* **recombinant DNA technology**.
- **Darbepoetin** [dar-be-POE-e-tin] is a ***modified form*** of **Erythropoietin** that is ***more heavily*** **glycosylated** with ***long-acting*** and ***delayed* onset of action** (half-life about three times that of epoetin alfa, it have no value in acute treatment of anemia).
- **Methoxy polyethylene glycol-epoetin beta**; is an ***isoform*** of **Erythropoietin** covalently attached to a long polyethylene glycol polymer with ***longer*** **half-life**.
- ***Administration*** (IV and SC).
  - **Epoetin alfa**; three times a week.
  - **Darbepoetin**; weekly.
  - **Methoxy polyethylene glycol-epoetin beta**; 2-week or monthly intervals.
- ***Uses***; **Anemia *associated with***; **end-stage renal disease** (not cleared by dialysis), **HIV**, **bone marrow disorders**, **prematurity** and **cancer**.
- ***Supplementation*** with **iron** may be *required to **ensure*** an **adequate response**.
- ***Dosages*** are ***adjusted*** to ***maintain*** a **target hemoglobin** up to, ***but not exceeding***, 10–12 g/dL (usually observed in about 10 days and an increase in hematocrit and hemoglobin levels in 2–6 weeks).
- ***Most common side effects***; **hypertension** and **thrombotic complications**.
- ***FDA warning***; in March 2007, the FDA issued a warning that **patients *with* chronic renal failure** or **cancer** whose ***serum*** **hemoglobin** is *raised to **more than*** **12 g/dL *with an* rhEPO** have ***greater*** **risk** of a **thrombotic event** **or**, in ***patients*** with ***advanced*** **head and neck cancers**, ***faster*** **tumor growth**.

Iron Supplements

- **Iron** is ***stored mostly*** in the **liver** as **ferritin** (iron-protein complex) *until needed by* the **body, iron** is ***delivered*** to the **marrow** for **hemoglobin production** by a ***transport*** **protein**, ***namely*** **transferrin.**
- **Iron deficiency anemia (IDA)** ***results from*** **acute** or **chronic blood loss**, from ***insufficient*** **intake** *during* periods of ***accelerated growth*** in **children**, and in ***heavily*** **menstruating** or **pregnant women.**
- **Iron** can be ***supplemented by*** the **oral route** or **parenteral route**;

Oral Iron Formulations

Ferrous Sulfate
Ferrous Gluconate
Ferrous Fumarate
Polysaccharide-iron Complex
Carbonyl Iron

- A ***wide variety*** of **oral iron preparations** is ***available.***
- Because **Ferrous Iron** is ***most efficiently*** **absorbed, ferrous salts** ***should be used.***
- **Ferrous Sulfate, Ferrous Gluconate** and **Ferrous Fumarate** are ***all effective*** and ***inexpensive*** and are ***recommended for*** **most patients.**

Pharmaco Kinetics

- **Absorption; acidic conditions** in the **stomach** *keep* **iron** in the **reduced Ferrous** form, which is the ***more soluble*** form (if iron stores are adequate, less will be absorbed).
- *About* **50-100 mg** of **iron** can be ***incorporated*** into **hemoglobin daily, *but*** only ***about*** **25%** of **oral ferrous iron salt** can be **absorbed.**

Guidelines

- **Centers for disease control and prevention (CDC)** ***recommendations***;
  - *For* **infants**; 2-4 mg/kg/day of iron drops.
  - *For* **school-age children** and **adolescent boys**; 60 mg/day of iron.
  - *For* **adults, adolescent girls** and **pregnancy**; 60-120 mg/day of iron.
  - *For* ***primary prevention*** during **pregnancy**; 30 mg/day of iron.

- ***Repeat*** **the anemia screening** in ***after*** **4 weeks** of **iron supplements** → ***increase*** in **Hb concentration** of *greater than* or *equal* to **1 g/dL** → **iron-deficiency anemia** is ***confirmed***, ***continue*** **iron treatment** for **2 more months**, then ***recheck*** **Hb concentration** or **Hct** (***usually*** **3–6 months**).

Side Effects

- ***Common*** **side effects** (*dose-related*); **GI disturbances** *caused by local irritation* (**nausea, abdominal cramps, constipation** {if astringent} or **diarrhea** {*if irritant*}) and **dark stools.**
- Some patients have less severe GI adverse effects with one iron salt than another.

Drug Interactions

- **Iron** ***reduce*** **absorption** of **Levothyroxine.**
- **Iron** ***reduce amount of*** **Levodopa** & **Methyldopa** *available to the body.*
- **Proton pump inhibitors** ***reduce*** **iron absorption** (*reduce the acidity*).

Lactoferrin (Pravotin®)

- **Lactoferrin (LF)** is ***one of*** the **transferrin proteins** that ***transfer*** **Iron** to the **cells** and ***control*** the *level* of ***free*** **Iron** in the **blood.**
- **Lactoferrin** is ***widely represented*** in various ***secretory fluids*** (such as **milk**) and in **neutrophils.**
- It has **antimicrobial activity** (*decrease free iron for microbial growth*) and shows some **antiviral activity.**
- It has **anti-inflammatory, antioxidant** *activity and may* ***inhibits*** **growth** of **some cancers.**
- **Lactoferrin** can be ***purified*** from **milk** or ***produced*** **recombinantly.**
- ***Administration*** of **30% Lactoferrin** ***saturated with*** **Iron** (*called* **Bovine Lactoferrin**) (Pravotin®) can ***used to*** correct **iron deficiency anemia** with ***less*** **GI side effects** (70% of product ***contain*** **free Lactoferrin** can ***correct*** **excess free Iron** and ***decrease*** **free Iron GI side effects**) than ***other traditional*** **Iron salts.**

Parenteral Iron Formulations

Iron Dextran (CosmoFer®)	**Iron Sucrose** (Venofer®)
Sodium Ferric Gluconate Complex (Ferrlecit®)	**Ferumoxytol** (Feraheme®)
Iron Carboxymaltose (Ferinject®)	**Iron Isomaltoside -1000** (Monofer®)

- **Parenteral iron therapy** ***should be reserved for*** **patients** with **iron deficiency** *who are*;
  - * ***Unable to*** **tolerate oral iron.**
  - * ***Unable to*** **absorb oral iron.**
  - * ***Extensive*** **chronic anemia** (such as **chronic kidney disease**).
- **Parenteral administration** ***treats*** **IDA** ***rapidly***, ***but produces*** **serious dose dependent toxicity.**
- **Iron Dextran** (low-and-high-molecular weight) can be given by **deep IM or IV infusion** (IV is most commonly due to local pain and tissue staining that occur with the IM), *due to risk of* a **hypersensitivity** reaction *with* **Iron Dextran, allergy test** ***should be*** **confirmed** ***before*** **administration.**
- **Sodium Ferric Gluconate Complex** and **Iron Sucrose** are ***given only*** by the **IV route**. They appear to be ***less likely*** to cause **hypersensitivity reactions** (due to high-molecular-weight).
- ***Dose calculation***; Volume of product required (mL) = [weight (kg) x (14 - Actual Hb) x (2.145)] / C
  - Where C= concentration of elemental iron (mg/ml) in the product being used:
  - Iron dextran: 50 mg/mL. Iron sucrose: 20 mg/mL. Ferric gluconate: 12.5 mg/mL
- ***Chronic use*** of **parenteral iron**, it is important to ***monitor*** **iron storage** ***levels*** to ***avoid*** the **serious toxicity** ***associated with*** **iron overload.**
- ***Side effects*** of ***IV*** **Iron Dextran** ***therapy***; **headache, fever, arthralgias, nausea** and **vomiting, back pain, flushing, urticaria, bronchospasm,** and **rarely anaphylaxis** and **death.**
- ***Newer iron complexes***; can be *administered at* ***much*** **higher doses** ***than*** the **older complexes** with ***very low levels*** of **free iron** (low incidence to iron overload or toxicity) and ***do not require*** **test doses.**
  - **Ferumoxytol** [FER-ue-MOX-i-tol];
    - It was specifically *designed to* ***reduce*** **immunological reactivity** (***no allergy test***).
    - It can be ***rapidly*** *administered* (IV rate of **30–60 seconds**) as a 510 mg dose with the **second IV injection** administered 2 to 8 days later.
  - **Ferric Carboxymaltose** [FER-ik-kar-box-ee-MAWL-tose];
    - It is a ***newer formulation*** of **parenteral iron** which is ***consists of*** a **ferric hydroxide core** ***stabilized by*** a **carbohydrate shell**, allows for ***controlled delivery*** of **iron to target tissues.**
    - **Dose; 15 mg/kg IV** ***up to*** **1000 mg** may *repeat* **weakly.**
    - ***Minimum*** **administration time**; </=15 minutes.
    - ***Repeated weekly***; **not result** in ***accumulation*** in patients.
    - ***No*** **allergy test.**
  - **Iron Isomaltoside**;
    - It is a ***newer formulation*** of **parenteral iron** that has a **matrix structure** that *results in* ***very low levels*** of **free iron** and **labile iron.**
    - **Dose**; ***higher doses***, **20 mg/kg** in a ***single visit*** (can cause iron correction in a single visit), ***may repeat*** **once** after **weak** (based on clinical judgement).
    - ***Minimum*** **administration time**;
      - **IV infusion**; ≤ 1000mg > 15 minutes -> 1000mg ≥ 30 minutes
      - **IV injection**; 500 mg over 2 minutes.

Toxicity

- ***Acute Iron Toxicity***;
  - ***Acute ingestion*** of **10 tablets** of any commonly **oral iron preparations** can be ***lethal*** in **young children**;
    - **Necrotizing gastroenteritis**, with **vomiting, abdominal pain** and **bloody diarrhea** *followed by* **shock, lethargy** and **dyspnea.**
  - ***Urgent treatment*** **is necessary; Whole bowel irrigation** and *administration* of **iron-chelating agent** such as **Deferoxamine** (***N.B.***; Activated charcoal does not bind iron and thus is ineffective).
- ***Chronic Iron Toxicity*** (***Iron Overload***);
  - It is also known as **hemochromatosis**; results when ***excess iron*** is ***deposited*** in the **heart, liver, pancreas** and **other organs.** It can lead to **organ failure** and **death.**
  - It ***most commonly*** occurs in **thalassemia.**

Toxicity

- ***Clinical manifestations***;
  - Liver disease (hepatomegaly, 13%, cirrhosis 13%).
  - Skin bronzing or hyperpigmentation (70%).
  - Diabetes mellitus (48%).
  - Amenorrhea, impotence, hypogonadism.
  - Cardiomyopathy.
  - Arthropathy, osteopenia and osteoporosis.
  - Hair loss.
  - Koilonychia (spoon nails).
- ***Treatments***; the goal of therapy is to remove the iron before it can produce irreversible parenchymal damage;
  1) **Phlebotomy**; Once diagnosed blood is removed (phlebotomy), weekly phlebotomy; 7 mL/kg/phlebotomy (not to exceed 550 mL).
  2) **Chelation therapy**; In patients with hemochromatosis and heart disease, anemia, or poor venous access (see next).
  3) **Surgical procedures**; In end-stage liver disease & severe arthropathy.

Iron Chelation Therapy

- *Chelation therapy*; is a **medical procedure** that involves the ***administration*** of ***chelating agents*** to ***remove*** **heavy metals** ***from the*** **body**.
- ***Most common forms*** of **heavy metal** intoxication; **iron**, **lead**, **arsenic**, **copper** or **mercury**.

Deferoxamine (Desferal®)

- **Deferoxamine** [de-fer-OX a-meen] is a ***parenteral iron chelator***.
- It acts by ***binding*** **free iron** in the **bloodstream** and ***enhancing*** its ***elimination*** in the **urine**.
- ***Administration***; Parenteral (IV, IM or SC).
- ***Affinity***; *theoretically*, **100 parts** by weight of **Deferoxamine** is capable of ***binding approximately*** **8.5 parts** by weight of **ferric iron**.
- ***Contraindication***; **severe renal disease** or **anuria** (drug & the iron chelate, excreted primarily by kidney).

Deferiprone (Ferriprox®)

- **Deferiprone** [de-FER-i-prone] is an ***oral iron chelator***.
- ***Administration***; Oral (3 times a day).
- ***Affinity***; **3 molecules** of **Deferiprone** are ***capable of*** **binding** to **1 atom** of **Iron**.
- ***Warning***; **Deferiprone** ***may cause*** **fatal agranulocytosis**.

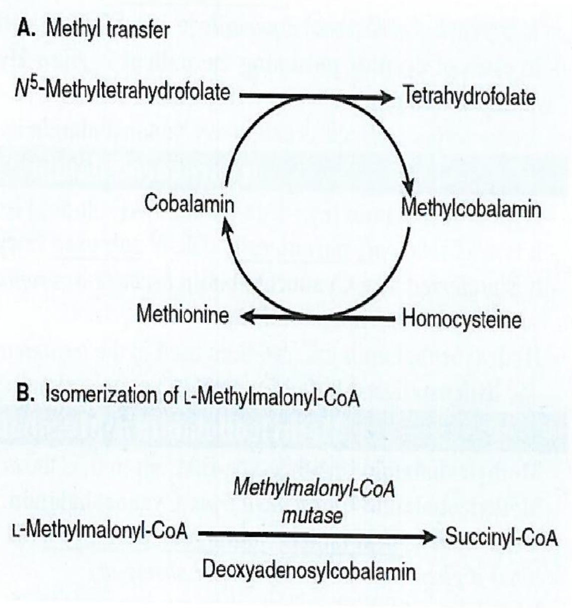
Deferasirox (Exjade®)

- **Deferasirox** [de-FER-a-sir-ox] is an ***oral iron chelator***.
- ***Administration***; Oral (once daily).
- ***Affinity***; ***2 molecules*** of **Deferasirox** are ***capable of*** **binding** to **1 atom** of **Iron** which are subsequently ***eliminated by*** **faecal excretion**.
- ***Warning***; **Deferasirox** ***may cause*** **severe** and *sometimes* **fatal kidney problems** or **liver problems**.

- *N.B.*;
  - ***Patients with*** **iron overload** usually ***become*** **vitamin C deficient**, *because* **iron** ***oxidizes*** vitamin C, **vitamin C** in doses > **200 mg** for **adults** may be given in ***divided doses***, starting ***after*** an **initial month** of ***regular treatment*** with ***iron chelator***.
  - **Iron Binding Dendrimers**; is a ***novel*** **iron(Fe^{3+})-selective chelator** capable of ***removing*** **dietary iron** *from the* **GIT** and ***preventing*** the *development of* **iron overload** typical of **haemochromatosis** and **thalassaemia**.

Vitamin B12 Supplements

- **Vitamin B$_{12}$** ***serves as*** a **cofactor** for ***several essential*** **biochemical reactions** in **humans.**
- **Intrinsic factor**, a protein *secreted by* the **stomach** that is *required for* **gastrointestinal uptake** of dietary **vitamin B$_{12}$.**
- ***Deficiency of*** **Vitamin B$_{12}$** ***leads to*** **megaloblastic anemia**, **gastrointestinal symptoms** and **neurologic abnormalities** (tingling "pins and needles" in the hands and feet).
- ***Two*** **essential enzymatic reactions** in **humans** *require* **Vitamin B$_{12}$**;


A. Methyl transfer
N^5-Methyltetrahydrofolate
Tetrahydrofolate
Cobalamin
Methylcobalamin
Methionine
Homocysteine
B. Isomerization of L-Methylmalonyl-CoA
Methylmalonyl-CoA mutase
L-Methylmalonyl-CoA
Succinyl-CoA
Deoxyadenosylcobalamin

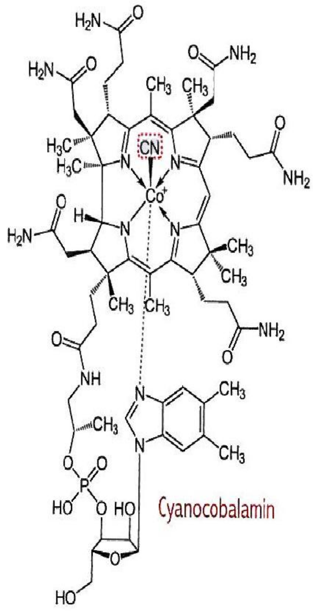
A) Serves as an intermediate in the transfer of a methyl group from N^5-methyltetrahydrofolate to homocysteine, forming methionine;

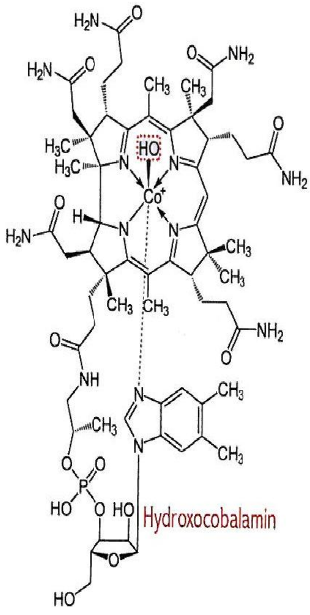
- As a result, Vitamin B$_{12}$ deficiency leads to deficiency of folate cofactors necessary for several biochemical reactions supplies DNA synthesis in rapidly dividing cells.
- The increase in serum homocysteine can be used to help establish a diagnosis of Vitamin B$_{12}$ deficiency elevated serum homocysteine increases the risk of atherosclerotic cardiovascular disease.

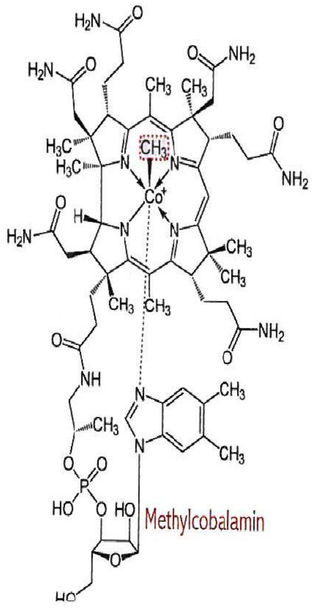
B) Vitamin B$_{12}$ is isomerization of methylmalonyl-CoA to succinyl-CoA by the enzyme methylmalonyl-CoA mutase;

- The increase in serum and urine concentrations of methylmalonic acid can be used to support a diagnosis of Vitamin B$_{12}$ deficiency.

- ***Initial therapy*** **100–1000 mcg** of **vitamin B$_{12}$ IM every other day** for **1–2 weeks** to ***replenish*** **body stores.** ***Maintenance therapy***; of **100–1000 mcg** of **vitamin B$_{12}$** IM ***once*** a **month for life.**
- ***Various*** **organic groups** may be ***covalently*** **bound** to the **cobalt atom**, *forming different* **cobalamins**; *such as* **Cyanocobalamin**, **Hydroxocobalamin** and **Methylcobalamin**.


Cyanocobalamin


Hydroxocobalamin


Methylcobalamin

Cyanocobalamin (Betolvex®)

- **Cyanocobalamin** [sigh-an-oh-koe-BAL-uh-min] is a **Vitamin B_{12} prodrug**.
- It is ***available***; **oral tablets**, **sublingual**, **parenteral** (**IM** and **SC**, not given IV due to it results in more rapid excretion) and **nasal spray** (Naso-cyanocobalamin®).
- It is the ***cheapest price of all*** and it is the ***most widely used*** *form of* **Vitamin B_{12}**.
- ***Due to*** it is ***rapidly excreted*** into the **urine**, it is also available in the ***protein-bound formulation*** such as **Cyanocobalamin Zinc Tannate** (Betolvex®) to ***improve*** **Cyanocobalamin kinetics**.
- **Cyanocobalamin** is *converted to* the **active form**, **"Methylcobalamin"** by **glutathione** and **other enzymes** and **co-factors**, *much higher dose* of **Cyanocobalamin** may cause **cyanide toxicity** (*due to depletion of glutathione*) *especially* in **renal failure patients**.
- In cases of **cyanide poisoning** the **patient** is ***given*** **Hydroxocobalamin**, which is a ***precursor to*** **Cyanocobalamin.**
- A ***very serious allergic reaction*** to **Cyanocobalamin** is ***rare***.

Hydroxocobalamin (Depovit-B_{12}®)

- **Hydroxocobalamin** [hye-drox-oh-koe-BAL-uh-min] is ***another*** **Vitamin B_{12} prodrug**.
- It is ***available***; ***only*** **parenterally** (**IM**), **IV** **only used** *for* ***cyanide poisoning***, *dose 5 g infusion in 15 min.*
- It is ***preferred*** than **Cyanocobalamin** ***because*** it is ***rapid response*** and ***more highly*** **protein-bound** and therefore has ***longer half-life***.
- **Hydroxocobalamin** has also been used in the ***treatment*** of **cyanide poisoning**. **Cyanide** ***displaces*** the **hydroxo** ligand forming a ***stable*** **Cyanocobalamin**.

Methylcobalamin or Mecobalamin (Methycobal®)

- **Methylcobalamin** [me-thile-koe-BAL-uh-min] is the ***active form*** of **Vitamin B_{12}**.
- **Methylcobalamin** is ***produced from*** **Cyanocobalamin**.
- It is ***available***; **oral tablets**, **sublingual**, **parenteral** (**IM** or **IV**) and **nasal spray**.
- It has ***higher*** **bioavailability** (***better absorbed***).
- It has a ***longer retention*** in **tissues** (*only one third of its dose is excreted*).
- **Methylcobalamin** is the ***only form*** of **Vitamin B_{12}** that ***can cross*** the **blood-brain barrier** ***without*** **assistance** or **conversion**;
    - Its **methyl group** ***stimulates*** **Serotonin** ***production*** in **CNS** (**mood support**).
    - ***High doses*** of **Methylcobalamin** have also been used to ***effective*** in **multiple sclerosis**.

Cobamamide

- **Cobamamide**; also ***known as*** **Adenosylcobalamin**, is an ***along with*** **Methylcobalamin**.

- ***N.B.***;
    - **Cobalamins** has been ***assigned to*** **pregnancy category C** by the FDA, ***do not*** **administer Cobalamins**, ***preserved*** with **Benzyl Alcohol** to **pregnant women** (**Benzyl Alcohol** has been ***associated with*** **serious adverse events** and **death**).
    - ***Large amounts*** of **Folic acid** (>1,000 µg/daily) can ***mask*** the **damaging effects** of **vitamin B_{12}** ***deficiency*** by ***correcting*** the **megaloblastic anemia** *caused by* **vitamin B_{12}** ***deficiency*** ***without*** **correcting** the **neurological damage** that *also occurs*.

Folic Acid (Folate) Supplements

- **Humans** ***cannot make*** **folates**; *therefore*, **Folic acid** (**Vitamin B_9**) has to be ***supplied*** through the **diet**. The **human body** ***needs*** **folate** to ***make*** **DNA**, ***repair*** **DNA** and ***methylate*** **DNA** as well as to act as a **cofactor** in ***certain*** **biological reactions**.
- ***Folate deficiency*** (***megaloblastic anemia***) may be *caused by*;
  1) **Increased demand** (*pregnancy and lactation*).
  2) **Poor absorption** (*disorder in small intestine*).
  3) **Alcoholism**.
  4) **Drugs that are dihydrofolate reductase inhibitors** (**Methotrexate**, **Pyrimethamine** and **Trimethoprim**).
- **Folic acid** is an ***oxidized form***, it must be ***converted to*** **active form** **Tetrahydrofolate** (**Tetrahydrofolic acid**) in the ***body*** by **dihydrofolate reductase (DHFR)** ***enzyme***.
- *Notes*;
  - **Folic acid** **intake** ***during*** **pregnancy** has been ***linked to*** a ***decrease*** **risk** of **neural tube defects** (**spina bifida**) and some ***other specific*** **kinds** of **birth defects**.
  - **Folate** is ***necessary for*** **fertility** in ***both*** **men** and **women**.
  - **Folic acid** appears to ***reduce*** the **risk** of **stroke** due to ***decrease*** **homocysteine concentration**.
  - **Folic acid supplementation** ***may slightly increase*** the **risk** of **some cancers**.

Folic Acid

- **1mg** of **folic acid** ***orally daily*** is **typically sufficient** to ***reverse*** **megaloblastic anemia** (it may administrated parenterally; IM, SC and IV).
- ***Usual adult dose for*** **folic acid deficiency**; **400-800 mcg**.
- **WARNING**; **Folic acid** ***should not*** be **given** ***alone*** in ***patients with*** **pernicious anemia** ***without*** **knowing whether** they also have a **Vitamin B_{12} deficiency**.

Drugs for Sickle Cell Disease

Hydroxyurea (Hydrea®)

- **Hydroxyurea** [high-DROX-ee-YOURee-ah] is an ***antineoplastic drug*** ***used in*** **polycythemia vera** and **essential thrombocythemia**.
- It is also ***used to reduce the rate*** of **painful attacks** in **sickle-cell disease**.
- It is also ***used in*** **AIDS** (due to antiretroviral properties).
- ***In sickle cell disease***; **Hydroxyurea** ***increases*** **fetal hemoglobin levels**, thus ***diluting*** the **abnormal hemoglobin S (HbS)** (*this process takes several months*).
- ***Most common serious side effects***; **bone marrow suppression** and **cutaneous vasculitis**.

Pentoxifylline (Trental®)

- **Pentoxifylline** [PEN-tox-IF-i-lin] is a ***methyl-xanthine derivative*** that ***inhibits*** **phosphodiesterase enzyme** and ***affects*** **blood rheology**. It has been called a "***rheologic modifier***"
- It ***improves*** **blood flow** by ***increasing*** **erythrocyte** and **leukocyte** ***flexibility***. It also ***inhibits*** **platelet aggregation**.
- **Mechanism of action**; It inhibits erythrocyte phosphodiesterase, resulting in an increase in erythrocyte cAMP activity ⇨ erythrocyte membrane becomes more resistant to deformity. Along with erythrocyte activity, it also decreases blood viscosity by reducing plasma fibrinogen concentrations and increasing fibrinolytic activity. It is also a non-selective adenosine receptor antagonist.
- It is ***used*** in the treatment of **peripheral vascular diseases** and in the **management of cerebrovascular insufficiency**.
- It is ***used*** in patients with **intermittent claudication** (due to chronic occlusive arterial disease of limbs).
- It is ***also effective*** in **venous ulcer** with compression therapy.
- *Dose*; 400 mg orally 3 times a day.

- ***N.B.***; ***Other managements*** depend on **progression of disease**: **Preventing infections** (antibiotics; usually long acting penicillin), **anemia agents** and **stem cell** or **bone marrow transplants**.

B) Myeloid Growth Factors

Granulocyte Colony–Stimulating Factors (G-CSF)

- **Granulocyte Colony–Stimulating Factors** (**G-CSF**); is a ***glycoprotein*** that ***stimulates*** the **bone marrow** to *produce* **granulocytes** and **stem cells** and ***release them into*** the **bloodstream.**

Filgrastim (Neupogen®) (Zarxio®) | Tbo-filgrastim (Granix®) | Peg-filgrastim (Neulasta ®)

- **Filgrastim** [fil-GRAS-tim] is a ***granulocyte colony-stimulating factor*** (***G-CSF***) ***analog.***
- It is *produced by* ***recombinant*** **DNA technology, G-CSF** ***regulates*** the **production** of **neutrophils** *within the* **bone marrow**.
- **Tbo-filgrastim** [TBO-fil- GRAS-tim] have ***slight*** **structural differences** than **Filgrastim**, the pharmacokinetic, safety and efficacy ***don't significantly differ***.
- **Peg-filgrastim** [pegfil-GRAS-tim] (*linked to* polyethylene glycol) has a human ***half-life*** of **15-80 hours,** ***much longer than*** **Filgrastim** (**3-4 hours**).
- *Indications*;
  - **Neutropenia** *associated with* **congenital neutropenia, cyclic neutropenia, myelodysplasia** and **aplastic anemia.**
  - *Secondary prevention of* **neutropenia** *in patients undergoing* **chemotherapy.**
  - **Mobilization of peripheral blood cells in** ***preparation for*** **stem cell transplantation.**
- *Administration*; **Filgrastim**; IV or SC. **Tbo-filgrastim** and **Peg-filgrastim**; SC only.
- *Most common serious side effects*; **serious allergic reactions, bone pain** & *rarely* **splenic rupture.**

Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF)

Sargramostim (Leukine®)

- **Sargramostim** [sar-GRA-moe-stim] is a ***recombinant granulocyte macrophage colony-stimulating factor*** (***GM-CSF***).
- *Indications*; ***similar to*** those of **G-CSF**, *administration*; IV or SC.
- *Most common side effects*; **Fever, arthralgia** and **myalgia.**

C) Megakaryocyte Growth Factors

- **Megakaryocyte Growth** *and* **Development Factor** (**MGDF**), also *known as* ***Thrombopoietin*** (***THPO***); is a **glycoprotein hormone** *produced by* the **liver** and **kidney** which ***regulates*** the ***production*** of **platelets** by *stimulating* **megakaryocytes.**

Oprelvekin (Neumega®)

- **Oprelvekin** [oh-PREL-ve-kin] is ***recombinant*** **interleukin eleven** (**IL-11**), is a **thrombopoietic growth factor** that ***increase*** **platelet production.**
- **IL-11** is a member of a family of **human growth factors** and is being ***produced*** in the **bone marrow.**
- *Indications*; *Prevention* of **severe thrombocytopenia** & *secondary prevention* of **thrombocytopenia** *in patients undergoing* **chemotherapy.** *Administration*; SC.
- *Most common side effects*; **Fatigue, headache, dizziness, anemia, lung edema** and **arrhythmias.**

Romiplostim (Nplate®) | Eltrombopag (Promacta®)

- **Romiplostim** [ROM-i-PLOS-tim] is an ***analog*** of **thrombopoietin,** *approved for* treatment **chronic idiopathic** (*immune*) **thrombocytopenic purpura (ITP),** *administered* **weekly** intervals via **SC injection.**
- **Eltrombopag** [el-TROM-boe-pag] is an ***orally active small-molecule thrombopoietin-receptor agonist, approved for*** treatment **chronic idiopathic** (*immune*) **thrombocytopenic purpura (ITP).**